Editorial

Should inflammatory pathways be targeted for the prevention and treatment of hypertension?

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Hypertension is the most common modifiable risk factor for cardiovascular disease (CVD)[1] and is a leading cause of death globally.[2] Hypertension and CVD share common antecedent risk factors which include physical inactivity, obesity, and excess alcohol intake.[3] Though these established risk factors explain a large proportion of hypertension risk, its pathogenesis is still not fully established as it appears other additional life-style and genetic factors may be involved. There is therefore a need to identify and evaluate putative risk factors that may increase our knowledge of hypertension development, may have causal or predictive relevance, and which will help develop preventive and management strategies.

There is a wealth of evidence suggesting that inflammatory processes play a key role in the pathogenesis of coronary heart disease (CHD), which is the major manifestation of CVD.[4 5] It is reported that the process of atherosclerosis is characterised by a chronic, low-grade inflammatory process.[6] Indeed, both “upstream” (pro-inflammatory cytokines such as interleukin-1 (IL-1), IL-6, IL-18, tumour necrosis factor-α (TNF-α)) and “downstream” biomarkers (eg, C-reactive protein (CRP), fibrinogen) (**Table 1**) have consistently been demonstrated to be associated with CHD risk in several epidemiological studies (**Table 2**). Many “upstream” markers regulate the hepatic synthesis of “downstream” markers such as CRP and fibrinogen; however, IL-6 plays a central role in regulating the downstream inflammatory responsible for initiation and progression of the atherosclerotic process. Given the close link between hypertension and CVD and the established relationship between inflammation and CVD, it is plausible that inflammation would be linked to the risk of hypertension.

Based on the rationale that systematic inflammation may play a role in the development of hypertension and given the inconsistent evidence in the existing literature, Jayedi and colleagues performed a first literature-based systematic meta-analysis to assess the associations of circulating inflammatory markers with the risk of hypertension.[7] Using prospective and retrospective cohort designs, the authors evaluated the associations of

standard CRP, high-sensitivity CRP (hsCRP), IL-6 and IL-1β with hypertension risk. Where there was sufficient relevant data, the authors also performed a dose-response meta-analysis using restricted cubic splines. In total, 21 unique studies comprising of >140, 000 participants and >20,000 hypertension cases were included in the review.[7] Increased levels of CRP, hsCRP and IL-6 were each associated with an increased risk of hypertension, and these were consistent with linear dose-response relationships. In pooled analysis of three studies, there was no evidence of an association between IL-1β and hypertension. The magnitude of the effect of IL-6 was greater than that associated with CRP or hsCRP, though direct comparisons could not be performed. In addition, the associations of hsCRP and IL-6 with hypertension risk were not statistically significant when the studies were restricted to those results that controlled for body mass index (BMI). The authors attributed these findings to the limited number of studies available for pooling. However, given that adiposity is associated with increased systematic inflammation and there was no evidence that the association between CRP and hypertension was dependent on BMI, there remained the question of to what degree does obesity mediate the association between inflammation and hypertension.

The strengths of this meta-analysis include the comprehensive assessment of various inflammatory markers, employment of standardised risk estimates from all potential contributing studies to allow a consistent combination of estimates across studies, exploration of heterogeneity and several sensitivity analyses, subgroup analyses, and assessment of the dose-response relationships.[7] The limitations included (i) the restricted number of studies available for pooling for the majority of inflammatory biomarkers; (ii) the use of observational designs which are characterised by residual confounding, regression dilution bias, and do not establish causality; (iii) substantial between study heterogeneity in some of the comparisons; and (iv) the inability to show the impact of adjustment for all potential confounders and also combine models in studies that adjusted for the same set of confounders, because of the varying degree of adjustments across individual studies. In light

of the limitations, the authors called for caution when interpreting the results and recommended more research to elucidate the role of the evaluated inflammatory markers in the prevention and management of hypertension, with specific focus on whether they could be used as valuable screening tests for high-risk individuals.

In recent years, the assessment of cardiorespiratory fitness (CRF) has achieved significant clinical merit and is considered to be a vital part of CVD risk assessment. The growing body of evidence should be an impetus for all health care providers to incorporate CRF improvement as a high priority in the overall clinical treatment approach for patients with CVDs. Levels of CRF level have been shown to be strongly related to various clinical characteristics, including age, sex, body composition, quantity and quality of physical activity, smoking, inflammation and blood pressure. Physical exercise produces a short-term, inflammatory response, whereas regular exercise training studies demonstrate a long-term "anti-inflammatory" effect. This anti-inflammatory response may partly contribute to the beneficial effects of habitual physical activity on CVD outcomes including hypertension. In our previous study of inflammation, CRF, and hypertension,[8] we suggested that high CRF may attenuate the association between CRP and incident hypertension, especially among those with initially elevated CRP levels. Though there has been controversy regarding whether or not exercise training may reduce CRP levels independent of weight loss; clear evidence indicates that physical activity, improved CRF, and exercise training are associated with reductions in inflammation and CVD outcomes in both primary and secondary prevention populations.[9]

Despite some of the limitations, the current findings of Jayedi and colleagues are very relevant and may have several clinical implications.[7] They underscore potentially deleterious roles of increasing levels of CRP, hsCRP and IL-6 on the future risk of hypertension in the general population and are quite consistent with prior work in the arena of CVD. Unlike studies of CVD outcomes which have shown IL-1β, a ligand of the IL-1

family, to play a role in the pathogenesis of CVD;[10] the current meta-analysis of cohort studies demonstrated no evidence of an association between IL-1β and hypertension. The graded positive increase in hypertension risk with increasing levels of these inflammatory markers as well as the consistency of some of the associations, suggests causality; however, to demonstrate this requires robust evidence from randomised controlled trials (RCTs). Given the current evidence that both “upstream” and “downstream” inflammatory markers are associated with hypertension risk, supports the notion that the inflammation cascade may represent a potential causal therapeutic target. It has been reported that activation of the IL-1, IL-6, TNF-α pathway results in elevated levels of hepatic acute phase proteins, which include CRP, fibrinogen, and plasminogen activator inhibitor type-1.[11] Significant progress has been made in the arena of CVD using RCTs to test the inflammatory hypothesis of atherothrombosis using these pathways.[11] Canakinumab and methotrexate, two anti-inflammatory agents, inhibit production of IL-1, IL-6, and TNF-α as well as hepatic production of acute-phase proteins such as CRP.[11] In the recently published Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS), canakinumab at doses of either 150 mg or 300 mg administered once every 3 months resulted in a 39% reduction in hsCRP and a 15% reduction in major adverse cardiovascular events when compared with placebo.[12] However, canakinumab was associated with a higher incidence of fatal infections. Anti-inflammatory therapies may hold some early promise for CVD prevention and treatment; but would this be applicable for prevention and treatment of hypertension? It is still too early to say so as the current evidence is mostly based on observational data only. Whether inflammatory markers are more than just risk markers for hypertension needs to be resolved in future studies.

We appreciate and applaud the efforts of the authors for pooling the available evidence on inflammation and hypertension together. Indeed, as the authors have acknowledged in their conclusions, further work on inflammation and hypertension is needed. Other inflammation-related markers such as fibrinogen, TNF-α, leucocyte count, and albumin need to be

evaluated. Due to the limited number of studies available for pooling of individual data from different populations, large-scale studies are still required to confirm current findings. In the absence of RCTs, Mendelian randomisation studies of potential genetic variants related to levels of these inflammatory markers may provide another route to add knowledge on the causal relevance of inflammatory markers in the aetiology of hypertension. Though common "downstream" markers such as CRP and fibrinogen have been disregarded as causal mediators of CHD development, there is data to suggest that a causal relationship may exist between the "upstream" inflammatory markers and CHD, which is based on the findings that the genetic variant in the IL-6 receptor signalling pathway is associated with lifelong graded decreases in CRP and fibrinogen concentrations, as well as proportionate decreases in CHD events.[13 14] Whiles we await more convincing evidence on the potential relevance of inflammatory pathways in hypertension prevention, lifestyle measures such as engaging in regular physical activity; maintaining a good CRF level and healthy body weight; salt restriction; limitation of alcohol consumption; high consumption of vegetables and fruits; a low-fat diet; and elimination of smoking should remain the cornerstone for the primary prevention of hypertension.

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Table 1. “Upstream” and “downstream” markers of inflammation

“Upstream” biomarkers	**“Downstream” biomarkers**
Interleukin-1	C-reactive protein
Interleukin-6	Fibrinogen
Interleukin-8	Albumin
Interleukin-18	Leucocyte count
Tumour necrosis factor-α	Plasma and serum viscosity
Matrix metalloproteinase-9	Alpha1-antitrypsin
Soluble CD40 ligand	Alpha2-macroglobulin
	Lipoprotein-associated phospholipase A_2
	Plasminogen activator inhibitor type-1
	Amyloid A protein
	Monocyte chemoattractant protein 1
	Haematocrit
	Erythrocyte sedimentation rate
	von Willebrand factor

Table 2. Meta-analyses of prospective studies of inflammatory markers and cardiovascular outcomes

Author, year of publication [reference]	Inflammation marker	Outcome	No. of participants	No. of cases	Combined risk (95% CI)	Risk comparison reported
Danesh, 1998 [1]	Fibrinogen	CHD	NR	4,018	1.80 (1.60-2.00)	Top vs bottom third
	CRP	CHD	NR	1,053	1.70 (1.40-2.10)	
	Albumin	CHD	NR	3,770	1.50 (1.30-1.70)	
	Leucocyte count	CHD	NR	7,229	1.50 (1.40-1.60)	
Danesh, 2000 [2]	Haematocrit	CHD	NR	8020	1.16 (1.05-1.29)	Top vs bottom third
	Plasma viscosity	CHD	NR	1278	1.57 (1.34-1.85)	
	ESR	CHD	NR	1703	1.33 (1.15-1.54)	
Danesh, 2005 [3]	Fibrinogen	CHD	154,211	7,118	2.42 (2.24-2.60)	Per 1g/l increase in usual fibrinogen level
		Stroke		2,775	2.06 (1.83-2.33)	
		CVD		992	2.35 (2.21-2.49)	
Danesh, 2008 [4]	IL-6	CHD	24,768	5,730	3.34 (2.45-4.56)	Per 2-SD increase in usual IL-6 levels
Kaptoge, 2010 [5]	CRP	CVD deaths	136,912	3,430	1.82 (1.66-2.00)	Per 1-SD higher usual CRP levels
		CHD	91,990	5373	1.37 (1.27-1.48)	
		Ischaemic stroke	60,763	1931	1.27 (1.15-1.48)	
Kaptoge, 2014 [6]	IL-6	CHD	1514	833	1.25 (1.19-1.32)	Per 1-SD higher levels
	IL-18				1.13 (1.05-1.20)	
	MMP-9				1.07 (0.97-1.19)	
	sCd40L				1.07 (0.95-1.21)	
	TNF-α				1.17 (1.09-1.25)	
Kunutsor, 2016 [7]	Fibrinogen	SCD	25,553	388	2.07 (1.59-2.69)	Per 1-SD higher usual fibrinogen levels

CHD, coronary heart disease; CI, confidence interval; CRP, C-reactive protein; CVD, cardiovascular disease; IL, interleukin; MMP-9, matrix metalloproteinase-9; SCD, sudden cardiac death; SD, standard deviation; sCd40L, Soluble CD40 ligand; TNF, tumour necrosis factor

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