confounding factors [3]. Of note, the protective effect of diuretics appeared to increase with prolonged duration of use, and former use was associated with an increased risk up to 4 months after the last dispensed prescription.

These two studies in consort suggest that treatment with a thiazide type diuretic reduces the risk for osteoporotic fractures in hypertensive patients. This makes the results clinically relevant and potentially important. The post hoc analysis of ALLHAT [2] is the first large randomised controlled study in hypertension to demonstrate a benefit of diuretic treatment on incident fractures. However, that study excluded several patients with high risk for osteoporotic fractures such as coronary artery disease, chronic heart failure, and chronic kidney disease. Second, ALLHAT studied chlorothalidone, a preferred thiazide type diuretic in the United States, whereas hydrochlorothiazide or other diuretics are preferred in many countries. Third, at least one out of five patients assigned to chlorothalidone, amldipine, or lisinopril did not did not take their assigned drug class medication, and a similar proportion in the amldipine and lisinopril group patients took a diuretic at their five year follow up. Thus, the magnitude of the potential benefit of diuretic treatment on fracture risk may be difficult to assess from these results.

The large Swedish registry study [3] represents an unselected hypertensive population with more comorbidity than ALLHAT. Data were obtained from electronic health records and registries with minimal risk of selection bias; however, there was no formal protocol for data collection and follow up. Drug adherence was accounted for by use of data on dispensed drugs but, inherent to a retrospective cohort study there was no randomisation to treatment. Taken together, the results of these two studies extend previous findings of an association between antihypertensive treatment with thiazide type diuretics and an approximately 10-25% reduction in osteoporotic fractures [5,6]. Furthermore, the association between duration and timing of thiazide exposure and fracture incidence [3] may be taken to suggest a causal relation.

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**Hot Off the Press**

**Noriko Daneshtalab**  
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**Immune system regulation of hypertension evident in the homeostatic role of cyclooxygenase-2-derived PGE2 in response to increased dietary salt**

Hypertension on its own is a complex trait traditionally determined by both genetic and environmental factors with a high prevalence (~30% worldwide) and a major risk factor for other cardiovascular diseases.

Interestingly, it is also a disease which patients with autoimmune diseases such as psoriasis and arthritis are more prone to having at a higher prevalence than the normal population (1). These patients also have a significantly
higher cardiovascular morbidity and mortality (e.g. arrhythmia and stroke) compared to non-arthritic populations.

The use of nonsteroidal anti-inflammatory drugs (NSAIDS) by the autoimmune patients have been traditionally implicated in the increase in hypertension; the inhibition of cyclooxygenase (COX) 1 and 2 isozymes reduce renal blood flow, glomerular filtration rate, and cause sodium retention by reducing urinary sodium excretion particularly when sodium-loaded. In salt-sensitive subjects, this retention of sodium will cause blood pressure to rise (2) and may affect the BP-lowering effect of some antihypertensive medications (3, 4).

Considering the current surge in dietary salt intake in the developed countries, the actual role of COX inhibition and the role of the immune system in the mechanism of salt-sensitive hypertension development is an important avenue for investigation.

In that light, Zhang et al (5) from Raymond Harris’ research group have been looking at the mechanism by which COX-2 inhibition is associated with salt-sensitive hypertension and the important role of immune cells in its mediation. As macrophages express COX-2 and are a rich source of prostaglandins (PGs), they studied the multi-variate role of COX-2–derived PG expression and activity in Bone Marrow (BM)-derived cells in mediation of salt-sensitive hypertension.

Using various techniques and strains of mice such as C57BL/6 Cox2−/− and BM transplantation (BMT) from either WT or Cox2−/− males into syngeneic animals, their study indicated that with chronic salt loading, COX-2-generated PGs from BM-derived cells mediate BP homeostasis such that selective deletion of either COX-2 expression (Cox2−/− WT BMT) or PGE2 production (mPGES-1−/− WT BMT) in these cells increased predisposition to salt-sensitive hypertension.

Furthermore, selective deletion of the PGE2 receptor subtype EP4 in monocytes/macrophages also led to development of salt-sensitive hypertension, likely due to the net effect of an increase in macrophages as well as T cells and neutrophils in the kidney.

The lack of COX-2 or inhibition of EP4 signaling also altered macrophage/dendritic cell polarization, leading to a pro-inflammatory, or M1-like, phenotype rather than an anti-inflammatory, M2-like phenotype. Interestingly, both renal sodium chloride cotransporter (NCC) expression and phosphorylation were increased in mice with alterations in macrophage/dendritic cell COX-2 expression or activity, suggesting a role for PGs in direct regulation of NCC.

All in all, these studies suggest an important role of hematopoietic COX-2–derived PGE2 in both kidney and skin in maintaining the balance between pro- and anti-inflammatory responses to chronically increased dietary salt. Treatments that target COX-2 inhibition may predispose them to salt-sensitive hypertension.

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New Investigator Spotlight features for January and February 2017

January spotlight of the month
Yusuke Kobayashi
Yokosuka City Hospital; Visiting Researcher, Department of Medical Science and Cardiorenal Medicine, Yokohama City University Graduate School of Medicine; Director, The Kobayashi Medical Clinic, Japan.

Read an interview

February spotlight of the month
Brandi Wynne
Instructor of Medicine at Emory University, Atlanta, GA, USA (Department of Medicine, Renal Division)

Read an interview