Circulating active serum calcium reduces the risk of hypertension

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Abstract

Purpose: Calcium, which is one the most abundant mineral elements in the body, has been suggested to be involved in blood pressure regulation. We aimed to assess the association of active serum calcium (iCa) (which is the ionized and physiologically active form of serum calcium) with the future risk of hypertension.

Methods: Active serum calcium concentration was assessed at baseline in the Finnish Kuopio Ischemic Heart Disease population-based prospective cohort study of 1,562 normotensive men aged 42-61 years at baseline. Cox proportional hazard models were used to assess the hazard ratios (HRs) [95% confidence intervals (CIs)] for incident hypertension.

Results: During a median follow-up of 24.9 years, 247 men developed new onset hypertension. Active serum calcium was inversely associated with incident hypertension in an approximately linear fashion. In age-adjusted analysis, the hazard ratio for hypertension per 1 standard deviation increase in iCa was 0.86 (95% CI: 0.76-0.98), which remained consistent after adjustment for several established risk factors and potential confounders 0.82 (0.71-0.94). In a comparison of extreme quintiles of iCa levels, the corresponding adjusted hazard ratios were 0.59 (95% CI: 0.39 to 0.90) and 0.54 (95% CI: 0.35 to 0.82) respectively.

Conclusion: Active serum calcium is protective of future hypertension in a middle-aged male Caucasian population. Further research is needed to confirm these findings and help unravel the mechanistic pathways of calcium in the pathogenesis of hypertension.

Keywords

Active serum calcium; risk factor; blood pressure; hypertension

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Introduction

Calcium is one of the most abundant mineral elements in the body and only available to the body through dietary sources. It plays a major role in skeletal mineralization.[1] Approximately 50% of total serum calcium is in ionized form,[2] which is the physiologically active form of circulating calcium and a reliable indicator of calcium homeostasis.[3] In healthy subjects, total serum calcium concentration ranges from 2.2 to 2.6 mmol/l and the concentration of the ionized form is maintained within the range 1.10 to 1.35 mmol/l.[1] Increased serum levels of calcium have been demonstrated to be associated with the development of cardiovascular disease (CVD).[4] Calcium may be involved in the regulation of blood pressure and emerging evidence suggests calcium could play a role in the pathophysiology of hypertension, which is an established risk factor for CVD and used in cardiovascular risk assessment.[5] However, there is sparse and inconsistent data on the nature of the association between serum calcium and hypertension and majority of studies reporting on the associations have been based on case-control and cross-sectional designs. Some studies have shown higher concentrations of calcium to be associated with increased risk of hypertension,[6,7] whereas some have reported a protective effect,[8,9] and others have reported null associations.[10,11] In addition, these studies have relied on total or albumin-corrected estimates of serum calcium, which only approximate the levels of biologically active serum calcium (iCa).

To date, there has not been any prospective evaluation of the association between iCa concentrations and risk of hypertension; therefore the temporal sequence of the relationship is still uncertain. In this context, we aimed to assess the prospective nature of the association between iCa concentrations and incident hypertension in a population-based cohort of 1,562 apparently healthy middle-aged men from eastern Finland.

Methods

Study population comprised a representative sample of men aged 42-61 years recruited into the Finnish Kuopio Ischemic Heart Disease (KIHD) risk factor study.[12,13] The Research Ethics Committee of the

University of Eastern Finland approved the study, and each participant gave written informed consent. Assessment of risk factors and confounders, ascertainment of incident hypertension, and details of statistical analyses have been reported previously[14,15] and are described in the **Supplementary Material**. Briefly, the measurement of pH-corrected serum active calcium concentrations was made using ion selective electrodes (Microlyte 6, Kone, Finland; CV 1.6%). Incident hypertension was defined as a physician diagnosis of hypertension, SBP ≥ 140 mm Hg and/or DBP ≥ 90 mm Hg, or use of anti-hypertensive medication. Incident cases were ascertained by record linkage to the national hospital discharge registry and to the Social Insurance Institution of Finland register for reimbursement of medicine expenses used for hypertension. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated using Cox proportional hazard models. All statistical analyses were conducted using Stata version 14 (Stata Corp, College Station, Texas).

Results

The mean age [standard deviation (SD)] of normotensive participants at baseline was 53 (5) years. The mean (SD) baseline iCa concentration was 1.18 (0.05) mmol/l. During a median follow-up of 24.7 (interquartile range, 17.8-26.9) years, 247 new onset hypertension cases were recorded. In analysis adjusted for conventional risk factors (age, body mass index, systolic blood pressure, smoking status, history of diabetes, family history of hypertension, total cholesterol, high-density lipoprotein cholesterol, alcohol consumption, and physical activity), there was an approximately linear association between iCa concentrations and incident hypertension (**Figure**). The HR for hypertension per 1 SD increase in iCa was 0.86 (95% CI: 0.76 to 0.98) in age-adjusted analysis, which remained consistent in further analyses adjusted for established risk factors 0.87 (95% CI: 0.76 to 0.99) and additional adjustment for renal function, socioeconomic status, total energy intake, and serum zinc 0.82 (95% CI: 0.71 to 0.94). Alternatively, comparing the top versus bottom quintiles of iCa levels, the corresponding adjusted HRs were 0.59 (95% CI: 0.39 to 0.90), 0.60 (95% CI: 0.39 to 0.92), and 0.54 (95% CI: 0.35 to 0.82) respectively (**Table**).

Discussion

In this large-scale population-based prospective study of middle-aged Finnish men without a history of hypertension at baseline, baseline iCa concentration was approximately linearly and inversely associated with incident hypertension. The association was independent of several established risk factors for hypertension and other potential confounders.

Evidence linking serum calcium and blood pressure have been limited and the results mostly inconsistent. A number of mechanistic pathways have been postulated linking increased serum concentrations of calcium with the development of high blood pressure and these include: (i) serum calcium has been suggested to have a direct effect on blood pressure by its effect on the contractility of the vascular smooth muscle cells which contributes to peripheral vascular resistance;[16] (ii) alterations in intracellular calcium which determine the tension in vascular smooth muscle cells and also mediate the secretion of hormones such as catecholamines and angiotensin II, known to be involved in blood pressure control; (iii) calcium interacts with other ions such as magnesium, potassium, and sodium, which are involved in the regulation of blood pressure;[17] (iv) vasoconstriction of the renal vasculature which eventually leads to hypertension;[18] and (v) the effects of abnormal calcium levels on the blood pressure centers in the central nervous system.[11]

Though our current findings do not seem to reflect on the biological pathways proposed, there is a possibility that the protective effect demonstrated may reflect a true association for the following reasons: (i) the actual mechanistic pathways linking calcium and blood pressure are uncertain and most of these proposed pathways are speculative; (ii) in contrast to our study which demonstrated this association using iCa (regarded as the gold standard of calcium measurement[19]), previous studies linking raised calcium levels with increased blood pressure have relied on total or albumin-corrected serum calcium measurements, which can bias the calcium-blood pressure relationship. In addition, previous reports reporting positive relationships were conducted in studies that employed limited designs. The large-scale prospective nature of our study conducted in apparently healthy normotensive free-living individuals; the

high participation rate and no loss to follow-up; the long follow-up duration; and the detailed adjustment for a comprehensive panel of potential confounders, enhances the robustness of the results and minimises the likelihood of biases such as reverse causality and residual confounding, which were inherent in previous studies.; suggesting that there may be a true protective effect of iCa on the development of hypertension. Indeed, a number of observational and interventional studies have shown that calcium intake or supplementation is associated with blood pressure reduction.[20,21] Given that calcium is only available to the body through dietary sources, this suggests that the amount of calcium from dietary sources or supplements will correlate with total serum calcium and iCa concentrations. Though the mechanisms underlying the protective association are also not clear, a number of pathways have been suggested. Low calcium intake leading to low serum calcium levels, stimulates increased levels of parathyroid hormone (PTH);[1] which increases intracellular calcium concentrations leading to elevated blood pressure. Calcium also plays a role in the synthesis of prostaglandin, which has been demonstrated to influence the secretion of PTH.[22] Finally, calcium has also been shown to have a beneficial effect on lipid levels in both animal models and humans.[23,24] Our findings are relevant as they suggest that iCa might be protective of the risk of future hypertension. However, these results need to be interpreted with caution given limitations such as the relatively low event rate; lack of information on PTH and vitamin D; inability to correct for within-person variability in iCa levels due to absence of repeat measurements; and the lack of generalizability of the findings to other populations and age groups.

In conclusion, iCa is inversely and independently associated with future risk of hypertension in an approximately linear fashion in a middle-aged Finnish male population. Further research is warranted to replicate these results and help unravel the biological pathways linking calcium and blood pressure regulation.

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Declaration of Conflicting Interests

The authors declare that there is no conflict of interest.

Authorship

SKK and JAL conceived and designed the study. JAL acquired data. SKK analyzed and interpreted the data. SKK drafted the manuscript. SKK and JAL critically revised the manuscript for important intellectual content. JAL supervised the study. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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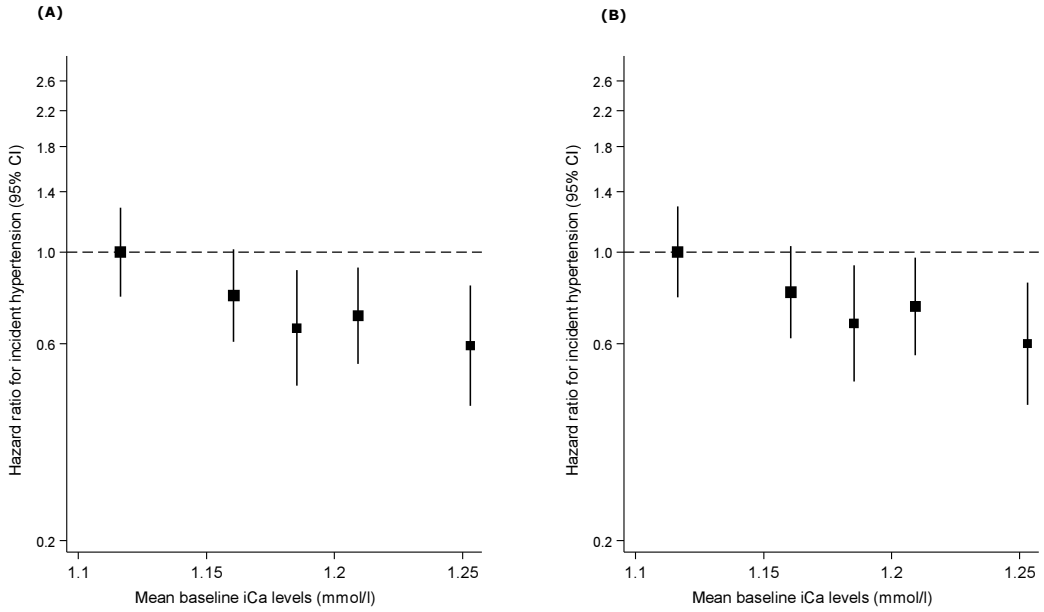
Figure legends

Figure. Hazard ratios for incident hypertension, by quintiles of baseline levels of active serum calcium



A, adjusted for age; **B**, adjusted for age, body mass index, systolic blood pressure, smoking, history of diabetes, family history of hypertension, total cholesterol, high-density lipoprotein cholesterol, alcohol consumption, and physical activity

iCa, active serum calcium

Table. Association of Active Serum Calcium and Incident Hypertension

Active serum calcium (mmol/l)	Events/ Total	Model 1		Model 2		Model 3	
		HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Per 1 SD increase	247 / 1562	0.86 (0.76 to 0.98)	0.019	0.87 (0.76 to 0.99)	0.029	0.82 (0.71 to 0.94)	0.005
Q1 (0.89-1.14)	63 / 318	ref		ref		ref	
Q2 (1.15-1.17)	59 / 375	0.78 (0.55 to 1.12)	0.182	0.80 (0.56 to 1.15)	0.224	0.78 (0.54 to 1.12)	0.174
Q3 (1.18-1.19)	37 / 264	0.65 (0.44 to 0.98)	0.041	0.67 (0.45 to 1.01)	0.059	0.61 (0.40 to 0.92)	0.019
Q4 (1.20-1.22)	53 / 351	0.70 (0.48 to 1.01)	0.058	0.74 (0.51 to 1.07)	0.110	0.66 (0.45 to 0.96)	0.031
Q5 (1.23-1.45)	35 / 254	0.59 (0.39 to 0.90)	0.014	0.60 (0.39 to 0.92)	0.019	0.54 (0.35 to 0.82)	0.005

CI, confidence interval; HR, hazard ratio; ref, reference; Q, quartile; SD, standard deviation

Model 1: Adjusted for age

Model 2: Model 1 plus body mass index, systolic blood pressure, smoking, history of diabetes, family history of hypertension, total cholesterol, high-density lipoprotein cholesterol, alcohol consumption, and physical activity

Model 3: Model 2 plus estimated glomerular filtration rate, socioeconomic status, total energy intake, and serum zinc