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Serum Calcium and Risk of Sudden Cardiac Arrest in the General Population

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Abstract

Objective: To evaluate the potential role of low serum Ca levels in the occurrence of sudden cardiac arrest (SCA) in the community.

Patients and Methods: We compared 267 SCA cases [177 (66%) men] and 445 controls [314 (71%) men] from a large population-based study (catchment population ~1 million individuals) in the US Northwest from February 1, 2002, through December 31, 2015. Patients were included if their age was 18 years or older with available creatinine clearance (CrCl) and serum electrolyte levels for analyses to enable adjustment for renal function. For cases, creatinine clearance and electrolyte levels were required to be measured within 90 days of the SCA event.

Results: Cases of SCA had higher proportions of blacks [31 (12%) vs 14 (3%); $P<.001$], diabetes mellitus [122 (46%) vs 126 (28%); $P<.001$], and chronic kidney disease [102 (38%) vs 73 (16%); $P<.001$] than did controls. In multivariable logistic regression analysis, a 1-unit decrease in Ca levels was associated with a 1.6-fold increase in odds of SCA (odds ratio, 1.63; 95% CI, 1.06-2.51). Blood Ca levels lower than 8.95 mg/dL (to convert to mmol/L, multiply by 0.025) were associated with a 2.3-fold increase in odds of SCA as compared with levels higher than 9.55 mg/dL (odds ratio, 2.33; 95% CI, 1.17-4.61). Cases of SCA had significantly prolonged corrected QT intervals on the 12-lead electrocardiogram than did controls (465±37 ms vs 425±33 ms; $P<.001$).

Conclusion: Lower serum Ca levels were independently associated with an increased risk of SCA in the community.

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It is estimated that approximately 300,000 individuals die of sudden cardiac arrest (SCA) annually in the United States.[1] However, more than half of men and close to 70% of women who die of SCA have no clinical history of heart disease before their cardiac arrest.[2,3] Hence, it is important to identify other risk factors and mediators for SCA to improve risk stratification and preventive strategies in the general population.

Electrolyte abnormalities are known to induce or facilitate clinical arrhythmia even in normal cardiac tissue, and they can lead to SCA.[4] Calcium is an essential cation for the myocardial action potential and excitation-contraction coupling of cardiac muscle.[5] Importantly, low serum Ca levels are associated with an increased risk of SCA in patients on dialysis.[6] However, the evidence for the relationship between Ca intake and cardiovascular events is mixed and at times contradictory. In some observational studies, a strong inverse or neutral relationship was noted between Ca intake and mortality from ischemic heart disease.[7,8] In addition, communities with a Ca-rich water supply seem to have a lower incidence of cardiovascular events.[9] In contrast, there are reports of an upward trend in cardiovascular event rates including myocardial infarction and sudden death in postmenopausal women who received Ca supplementation, resulting in higher blood Ca levels.[10,11] In summary, it is not clear whether blood Ca levels are related to SCA in the general population. Therefore, we evaluated the association between serum Ca levels and SCA in a large community-based study, also adjusting for renal function.

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PATIENTS AND METHODS

Case and control subjects were ascertained in the Oregon Sudden Unexpected Death Study, a prospective ongoing population-based study of SCA started on February 1, 2002, in the Portland, Oregon, metropolitan region (catchment population ~1 million individuals). The details of the design and ascertainment of cases and controls have been reported previously.[12,13] In brief, cases of out-of-hospital cardiac arrest are identified from multiple sources including county medical examiner's office, emergency medical response system (ambulance and fire services), and local hospital emergency departments. Cases also included survivors of SCA. Since 2002, the Oregon Sudden Unexpected Death Study has reviewed all SCAs with emergency medical response system response as well as additional cases from the medical examiner and hospitals. *Sudden cardiac arrest* was defined as a sudden unexpected pulseless condition if witnessed or unexpected death within 24 hours of last having been observed in the usual state of health if unwitnessed. Sudden cardiac arrest was adjudicated by 3 in-house physicians after reviewing all available medical records or autopsy reports for each subject,[12] and all SCAs meeting inclusion criteria were enrolled. Noncardiac etiologies such as trauma, chronic terminal illness, and drug overdose were excluded. Control subjects were enrolled during the same time period and from the same geographical region as the cases from multiple sources within the Portland metropolitan region, including emergency medical services that treated patients with chest pain, outpatient local hospital clinics, patients undergoing coronary angiogram at a participating hospital system, and a local large health maintenance organization (HMO). From the first 3 sources, all potential control subjects were identified, contacted, consented, and enrolled if they had documented *coronary artery disease* (CAD), defined by history of myocardial infarction, revascularization, or angiogram with 50% or more stenosis in a major coronary artery. Controls were excluded if they had a history of ventricular arrhythmia or SCA.[12] For HMO controls, a random sample of HMO members (half with documented CAD, half without) were frequency matched to cases by age and sex and were enrolled using the same procedures described above. The control population was selected to represent the source population of the cases, with a predominance of individuals with documented CAD to adequately control for CAD in case-control comparisons. Eighty percent of control subjects had a diagnosis of CAD to match the estimate of CAD among the cases reported in previous community-based studies.[14]

For both cases and controls, electrolyte levels were obtained from the results of clinical laboratory tests performed during routine clinical practice, if available in patients' medical records. Cases for this analysis were included if they were enrolled from February 1, 2002, through December 31, 2015, and their electrolyte levels were measured within the 90 days of SCA. Subjects were excluded if their age was less than 18 years or if there were no available creatinine clearance (CrCl), serum Ca, or serum albumin level measurements. The CrCl level was calculated using the Cockcroft-Gault formula.[15] Although free (ionized) Ca is more physiologically relevant than total Ca, measured ionized Ca was not available from most routine clinical laboratory test results. Therefore, serum Ca levels were corrected using the concomitantly measured serum albumin levels and using a widely used formula {corrected Ca level in mg/dL=uncorrected value in mg/dL+[0.8(4−albumin level in g/dL)]}.[16,17] Normal albumin levels were set at 4 g/dL (to convert to g/L, multiply by 10). Detailed clinical information was obtained for all subjects from review of all available medical records. The QT interval was measured from archived standard resting 12-lead electrocardiograms with a paper speed of 25 mm/s and a calibration of 10 mm/mV (before and unrelated to the cardiac arrest in cases) and corrected for heart rate using Bazett's formula. Only electrocardiograms performed within 90 days before the arrest were included.

For this analysis, laboratory test results obtained within 90 days of the arrest were chosen for SCA cases because results would indicate the patient's electrolyte status shortly before the arrest. Overall, cases with laboratory test results available within 90 days of arrest were somewhat older and had a higher comorbidity burden (mean age, 66.1 years;

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