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

To the Editor: We were pleased to read the article by Yarmohammadi et al[1] in the October 2017 issue of *Mayo Clinic Proceedings*, in which they reported an independent association between low calcium levels and an increased risk of sudden cardiac arrest (SCA). We applaud their methodology and focused exploration of possible causal mechanisms of cardiac arrest. However, we are concerned about the weak physiologic basis for their findings, the range of calcium values discussed in the article, and the potential harm to the general population if calcium levels become a target for intervention.

The physiologic basis for calcium being a major or direct cause of lethal arrhythmia is controversial, whereas other electrolytes, specifically magnesium and potassium, are closely associated with calcium levels and have a much stronger and consistent relationship with lethal arrhythmias. Moreover, although hypocalcemia alters the cardiac action potential and lengthens the QTc interval, these effects are rarely present near the generally accepted ranges reported by Yarmohammadi et al. In addition, the reported QT intervals do not support that hypocalcemia induced the observed arrhythmias. Although the difference in QT intervals between the cases and controls was statistically significant, the difference between calcium levels in these groups was clinically negligible, implying that calcium may not have been the only factor responsible for the observed QT difference. Even so, the observed QT difference was not likely clinically significant given the overall inaccuracy of measuring clinical QT intervals. Lastly, despite a 2.3-fold increase in the risk of SCA, there was no difference in QT intervals between the highest and lowest quartiles of calcium, suggesting that some unaccounted factor may have been responsible for the relationship.

Several factors associated with SCA and QT prolongation could be considered in this analysis, including a history of thyroid disease, elevated parathyroid hormone levels due to the high prevalence of chronic kidney disease, myocardial infarction, and the use of QT prolonging medications.[2,3] A major consideration would be magnesium levels, which were not available in this study.[4,5]

We applaud the skilled work the authors have conducted in this very important area. However, because of the concerns we outlined, the extrapolation of their findings to SCA prevention is premature. As the authors stated, evidence regarding the association between calcium and cardiac events is equivocal, and the evidence at present does not support a change in our understanding of the relationship between electrolyte abnormalities and SCA.

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

We appreciate the interest from Husain and colleagues in our recent article, in which we reported an association between lower levels of serum calcium and increased risk of sudden cardiac arrest (SCA). We will respond to each of their comments and also refer readers to the editorial by Lee[1] in the same issue, which we believe provides a balanced perspective on our findings.

To our knowledge, our work remains the first community-based study to report the association of lower serum calcium level with SCA. It is also important to recognize that measurement of serum calcium within 90 days of the SCA event is a unique aspect of our study. All of the previously published associations between serum electrolytes were performed using measurements in samples collected at baseline, ranging between approximately 5 and 15 years in advance of the SCA event.[2-4] It is difficult to know how relevant these remote measurements may have been to the distant SCA event. Because our case-control study design does not allow for direct causal inferences, we were careful not to make any. Given the complexity of the SCA phenotype, we agree that prolongation of the QTc is likely to be multifactorial and is a consistent finding in multiple populations including ours.

However, 10% higher values of the QTc in cases are well beyond what could be ascribed to measurement error. In fact, to illustrate this point, there are clinically established 2.5% higher values of the QTc in women compared with men (upper limits of normal, 450 ms in women vs 440 ms in men).[5] We agree that potential mechanisms by which serum calcium levels may affect SCA risk are poorly understood, but our findings should serve as an impetus for efforts to improve the understanding of this phenomenon. In this context, it is important to recognize that differences in serum calcium values in the "clinically normal" range could still have implications for pathophysiology. Today, the general consensus in the field for mechanisms of the SCA complex trait is that there are likely to exist multiple overlapping substrates, risk factors, and triggers. How can we exclude the possibility that moderately lower serum calcium could be a risk modifier? In fact, one of the reported associations between low magnesium levels and SCA that Husain et al refer to was also in the "clinically normal" range.[4] Moreover, none of these previous studies were able to adjust for serum calcium values. We could not adjust for magnesium levels but did account for other potential confounders including potassium levels, hypothyroidism, diabetes, creatinine clearance, use of diuretics, and left ventricular ejection fraction, and the association between serum calcium level and SCA remained robust.

We remain excited about the potential mechanistic and risk stratification implications of reporting this new association but certainly do not advocate for acting on these findings in terms of health promotion or SCA prevention without considerable further investigation.

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Cardiac Compromise in Zika Virus Infection

To the Editor: We have read with interest the case report of Schwartzmann et al[1] reporting a single case of Zika virus (ZIKV) meningoencephalitis, but also with ZIKV propagation to other organs, including the heart. As in other arboviral diseases (dengue and chikungunya),[2-4] cardiovascular disorders such as arrhythmias, among others, are being observed in previously healthy cases. But there is a lack of publications assessing it. We take this opportunity to discuss 2 cases of pregnant women from an endemic area (Sucre, Colombia), with confirmed ZIKV infection who presented with cardiovascular and electrocardiographical (ECG) alterations (myocarditis).

Case 1. Age 30 years, 34.2 gestational weeks, presenting with rash and pruritus. Zika-RT-PCR positive, negative for dengue and chikungunya. Her ECG showed a sinusal tachycardia with a prolonged QTc (associated with Torsade de Pointes) (using Bazett formula) (Figure A). Cardiac enzymes were negative. At the echocardiogram, 200 cc of pericardial fluid was found. She had not presented with cardiovascular disease earlier. After 2 weeks, ECGs and echocardiograms were normal.

Case 2. Age 25 years, 10.1 gestational weeks, presenting with rash and pruritus. Zika-RT-PCR positive, negative for dengue and chikungunya. Her ECG showed a left anterior hemiblock (Figure B). At the echocardiogram, 300 cc of pericardial fluid was found. Cardiac enzymes were negative. She had not presented with cardiovascular disease earlier. After 2 weeks, ECGs and echocardiograms were normal.

The ECG alterations were seen in patients, previously healthy and young patients, as well as also reported recently in congenital cases.[5] Although a large epidemic of ZIKV has affected the Americas, there is a lack of literature about cardiovascular manifestations in adult patients with ZIKV infection, including those who are pregnant. This would lead to prospective systematic ECG assessments in patients with ZIKV infection.[4] As has been recently proposed with chikungunya, in patients with suspicion of ZIKV infection, cardiovascular assessment and ECG should be routinely performed, especially in pregnant women.

Although this case report has limitations, it would be the first in the Caribbean region of Colombia and in the country, adding evidence that ECG alterations in patients with confirmed ZIKV infection would