COMMENTS AND RESPONSES

Comment on: Kromhout et al. n-3 Fatty Acids, Ventricular Arrhythmia–Related Events, and Fatal Myocardial Infarction in Postmyocardial Infarction Patients With Diabetes. Diabetes Care 2011;34: 2515–2520

We read the article by Kromhout et al. (1) with interest. The authors clearly suggest that low-dose supplementation of the n-3 fatty acids eicosapentaenoic acid, docosahexaenoic acid, and α-linolenic acid significantly reduces ventricular arrhythmia–related events in postmyocardial infarction patients with diabetes.

An abnormal cardiac repolarization, due to an imbalance of the autonomic nervous system, could link diabetes and cardiac arrhythmias, as an association was shown between autonomic neuropathy (AN) and abnormalities in sympathovagal balance and QT interval prolongation (2) in diabetic patients.

The sympathovagal balance, expressed as low frequency:high frequency (LF:HF) ratio, represents the most accurate measure of sympathovagal balance (2).

We have previously shown that acute hyperglycemia increases LF:HF ratio in patients with type 2 diabetes without AN and in healthy control subjects but not in diabetic patients with AN (2). We also demonstrated that glycemic variability is associated with an increased LF:HF ratio in newly diagnosed type 2 diabetic patients with good glycemic control and without AN (3). Hyperglycemia activates the sympathetic nervous system, probably through the activation of the oxidative stress pathway and a reduction of nitric oxide availability (4).

The lack of effects of hyperglycemia on the LF:HF ratio in patients with AN is likely related to the fact that, in the presence of AN, nitric oxide is already maximally reduced, following prolonged oxidative stress, and is not further influenced by hyperglycemia.

However, although in diabetic patients without AN, hyperglycemia is still able to induce a sympathetic stimulation, we have shown that it failed to increase corrected QT (QTc) interval. This blunted response of QTc to hyperglycemia observed both in patients with and without AN, suggests that the diabetic state per se causes a "dysautonomic state," possibly through the activation of mechanisms related to chronic hyperglycemia (oxidative stress, endothelial dysfunction) (2).

Omega-3 polyunsatured fatty acids (PUFAs) have been shown to increase resting heart rate variability (5), possibly through an enhanced baseline cardiac parasympathetic tone. Therefore, the cardiovascular benefits ascribed to dietary n-3 PUFAs could be due, at least in part, to the improvements in cardiac autonomic balance (5).

We demonstrated that a 6-month treatment with PUFA significantly decreases sympathovagal balance during the night and significantly increases the physiological nocturnal fall of QTc, in diabetic patients without AN but not in those with AN (2), probably because of an irreversible damage of the autonomic nervous system.

In conclusion, we suggest that the observation made by Kromhout et al. of a reduction in ventricular arrhythmia–related events in diabetic patients treated with a combination of icosapentaenoic acid, docosahexaenoic acid, and α-linolenic acid after a myocardial infarction can be explained by a reduction of sympathetic prevalence during the night and a restoration of normal cardiac conduction.

Our observation of a lacking effect of PUFA supplementation in patients with cardiac AN suggests that *1*) PUFA may represent a useful treatment in the prevention of abnormalities in cardiac conduction, only before the onset of irreversible damage of the autonomic nervous system; and *2*) diabetic AN should be considered when interpreting data from literature.

Ilaria Giordani, MD
Fabiana Picconi, MD
Ilaria Malandrucco, MD
Simona Frontoni, MD, PHD

From the Unit of Endocrinology, Diabetes and Metabolism, San Giovanni Calibita Fatebenefratelli Hospital, Rome, Italy; and the Department of Internal Medicine, University of Rome Tor Vergata, Rome, Italy.

Corresponding author: Simona Frontoni, frontoni@uniroma2.it.

DOI: 10.2337/dc12-0107

Acknowledgments—No potential conflicts of interest relevant to this article were reported.

References

1. Kromhout D, Geleijnse JM, de Goede J, et al. n-3 fatty acids, ventricular arrhythmia-related events, and fatal myocardial infarction in postmyocardial infarction patients with diabetes. Diabetes Care 2011;34:2515–2520
2. Santini V, Ciampittiello G, Gigli F, et al. QTc and autonomic neuropathy in diabetes: effects of acute hyperglycaemia and n-3 PUFA. Nutr Metab Cardiovasc Dis 2007; 17:712–718
3. Di Flaviani A, Picconi F, Di Stefano P, et al. Impact of glycemic and blood pressure variability on surrogate measures of cardiovascular outcomes in type 2 diabetic patients. Diabetes Care 2011;34:1605–1609
4. Marfella R, Nappo F, De Angelis L, Paolisso G, Tagliamonte MR, Giugliano D. Hemodynamic effects of acute hyperglycemia in type 2 diabetic patients. Diabetes Care 2000;23: 658–663
5. Christensen JH, Schmidt EB. Autonomic nervous system, heart rate variability and n-3 fatty acids. J Cardiovasc Med (Hagerstown) 2007;8(Suppl. 1):S19–S22