Letter by Menzaghi et al Regarding Article, “Plasma Levels of Fatty Acid–Binding Protein 4, Retinol-Binding Protein 4, High-Molecular-Weight Adiponectin, and Cardiovascular Mortality Among Men With Type 2 Diabetes: A 22-Year Prospective Study”

To the Editor:

We read with interest the article on the paradoxical association between high-molecular-weight (HMW) adiponectin and cardiovascular mortality in men with type 2 diabetes mellitus from the HPFS (Health Professional Follow-Up Study). These data resemble those we have previously reported in men with type 2 diabetes mellitus, comprising a large subset of the same HPFS- and additional Italian individuals. To address whether such association is sustained by a cause–effect relationship, a genetic risk score (GRS) built on 19 single nucleotide polymorphisms previously associated with adiponectin levels (Mendelian randomization) was used. Notably, GRS was not associated with cardiovascular mortality, thus speaking against a causal role of HMW adiponectin on it. This finding is in marked contrast with our recent report, showing a significant association between rs832354 (a single nucleotide polymorphism strongly associated with HMW adiponectin) and cardiovascular mortality in type 2 diabetes mellitus patients of both sexes. Of note, our association was entirely driven by males (ie, no association observed among females), thus coincidentally reinforcing the belief of a sexual dimorphic effect of serum adiponectin on cardiovascular mortality and further stressing the difference with Liu et al report.

Here, we address some possible causes of such striking discrepancy. First, differences in the clinical set may have played a role. In fact, although in HPFS only 50% patients had baseline cardiovascular disease, all our patients had established coronary artery disease. That this difference may be important is suggested by the observation that when in HPFS participants with baseline cardiovascular events were excluded, the hazard ratio (95% confidence interval) of cardiovascular mortality of patients with high HMW adiponectin decreased from 2.07 (1.42–3.06) to 1.39 (0.54–3.61), a 54% reduction in a log scale. It is, therefore, likely that in the absence of baseline cardiovascular disease, the deleterious effect of adiponectin on cardiovascular mortality is attenuated, thus making difficult addressing causality.

Second, also differences in environmental and genetic background across studies have to be considered. In fact, HPFS patients were recruited from all over the United States, whereas ours were all recruited in a very small and homogeneous region of Central Southern Italy. In addition, whereas our participants were all Whites, those of HPFS were not. Because genetic background of serum adiponectin is heterogeneous across ethnicities, such difference too may have contributed to discrepancy between the 2 studies.

Third, statistical power is important to make reliable Mendelian randomization studies. Unfortunately, in Liu et al article, no power was reported for the association between GRS and cardiovascular mortality. Because GRS was barely associated with HMW adiponectin ($P=0.02$), the risk of false-negative findings on its association with cardiovascular mortality has to be seriously considered.

Finally, it seems, also by the reference quoted (ie, 29, which reports a case–control study), that a logistic rather than a Cox regression was used when analyzing the association between GRS and cardiovascular mortality. If this is the case, ignoring time to event could have altered the results and contributed to the discrepancy with our study.

In all, disentangling the intrinsic nature of the paradoxical association between adiponectin and cardiovascular mortality in type 2 diabetes mellitus is a difficult task; further collaborative studies, in extensively phenotyped patients of different ethnicities from well-powered samples, are definitely needed to accomplish it.

Acknowledgments

This communication was supported by grants from the Italian Ministry of Health grants, RC2014, RC2015, RC2016, and RF-2013-02356459, European Foundation for the Study of Diabetes/Pfizer grants and Società Italiana di Diabetologia-Fondazione Diabete Ricerca (C. Menzaghi).

Disclosures

None.

Claudia Menzaghi
Research Unit of Diabetes and Endocrine Diseases
IRCCS Casa Sollievo della Sofferenza
San Giovanni Rotondo, Italy

Massimiliano Copetti
Unit of Biostatistics
IRCCS Casa Sollievo della Sofferenza
San Giovanni Rotondo, Italy

Vincenzo Trischitta
Research Unit of Diabetes and Endocrine Diseases
IRCCS Casa Sollievo della Sofferenza
San Giovanni Rotondo, Italy

Department of Experimental Medicine
Sapienza University of Rome
Italy

References


Letter by Menzaghi et al Regarding Article, "Plasma Levels of Fatty Acid–Binding Protein 4, Retinol-Binding Protein 4, High-Molecular-Weight Adiponectin, and Cardiovascular Mortality Among Men With Type 2 Diabetes: A 22-Year Prospective Study"

Claudia Menzaghi, Massimiliano Copetti and Vincenzo Trischitta

Arterioscler Thromb Vasc Biol. 2017;37:e55-e56
doi: 10.1161/ATVBAHA.117.309308
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2017 American Heart Association, Inc. All rights reserved.
Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://atvb.ahajournals.org/content/37/5/e55

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Arteriosclerosis, Thrombosis, and Vascular Biology can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Arteriosclerosis, Thrombosis, and Vascular Biology is online at:
http://atvb.ahajournals.org//subscriptions/