COMMENTS AND RESPONSES

Response to Comment on: Ellervik et al. Elevated Transferrin Saturation and Risk of Diabetes: Three Population-Based Studies. Diabetes Care 2011;34:2256–2258

We thank Conway for her comment (1) on our article in *Diabetes Care* (2) on the risk of diabetes associated with elevated transferrin saturation levels in two follow-up studies (risk as hazard ratios and exposure preceding disease) and a case-control study (risk as odds ratio) with neither study being cross-sectional.

We agree with Conway that the pathophysiology of diabetes is complex. We acknowledge that elevated cellular iron concentrations in insulin-sensitive tissue and the pancreatic β-cell, being primary causative elements of diabetes in hemochromatosis, may exert permissive or synergistic actions in the pathogenesis of both type 2 as well as autoimmune and nonautoimmune type 1 diabetes by promoting the formation of reactive oxygen species via the Fenton reaction. However, our study is an epidemiological risk marker study, not a cause-and-effect study or a pathophysiological study, and any pathophysiological interpretation of our findings is by nature speculative and hypothesis creating.

Iron overload is a storage disorder leading to iron deposition in various organs encompassing the pituitary and leading to decreased levels of several hormones including androgens, which would speak against the insulin-sensitizing effect of androgens in response to diabetes as proposed by Conway. Furthermore, individuals in the general population with decreased androgens within the normal level have increased risk of developing diabetes (3).

We cannot exclude that some individuals in our study with high transferrin saturation could have a bone marrow disorder with reduced or high iron turnover such as hypoplastic anemia or hemolytic disease, hepatocellular injury, or a transient nonspecific rise in transferrin saturation rather than increased iron stores; however, a significant contribution of such conditions is unlikely because of the rarity of these diseases. In individuals with iron overload, erythrocyte indices are slightly increased, primarily by increased iron uptake and hemoglobin synthesis by immature erythroid cells (4).

In conclusion, we believe that iron overload is the primary exposure, with a resultant cascade of other implications on organ dysfunction including hypogonadism and increased erythrocyte indices.

CHRISTINA ELLERVIK, MD, PHD[1,2,3]
THOMAS MANDRUP-POULSEN, MD, DMSCI[2,4,5,6]
HENRIK BIRGENS, MD, DMSCI[2,7]
BØRGE G. NORDESTGAARD, MD, DMSCI[1,2]

From the [1]Department of Clinical Biochemistry, Herlev Hospital, Copenhagen University Hospital, Herlev, Denmark; the [2]Faculty of Health Sciences, University of Copenhagen, Copenhagen, Denmark; the [3]Department of Clinical Biochemistry, Næstved Hospital, Copenhagen University Hospital, Næstved, Denmark; the [4]Center for Medical Research Methodology, University of Copenhagen, Copenhagen, Denmark; the [5]Department of Medicine and Surgery, Karolinska Institute, Stockholm, Sweden; the [6]Steno Diabetes Centre and Hagedorn Research Institute, Gentofte, Denmark; and the [7]Department of Haematology L, Herlev Hospital, Copenhagen University Hospital, Herlev, Denmark.

Corresponding author: Børge G. Nordestgaard, brno@heh.regionh.dk.

DOI: 10.2337/dc12-0382

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

References

1. Conway BN. Comment on: Ellervik et al. Elevated transferrin saturation and risk of diabetes: three population-based studies. Diabetes Care 2011;34:2256–2258 (Letter). Diabetes Care 2012;35:e47. DOI: 10.2337/dc12-0192
2. Ellervik C, Mandrup-Poulsen T, Andersen HU, et al. Elevated transferrin saturation and risk of diabetes: three population-based studies. Diabetes Care 2011;34:2256–2258
3. Selvin E, Feinleib M, Zhang L, et al. Androgens and diabetes in men: results from the Third National Health and Nutrition Examination Survey (NHANES III). Diabetes Care 2007;30:234–238
4. Barton JC, Bertoli LF, Rothenberg BE. Peripheral blood erythrocyte parameters in hemochromatosis: evidence for increased erythrocyte hemoglobin content. J Lab Clin Med 2000;135:96–104