Maternal Circulating Transthyretin Level Is Longitudinally Associated With Increased Risk of Gestational Diabetes Mellitus: It Is Not Just an Indicator of Nutritional Status

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Diabetes Care 2017;40:e53–e54 | DOI: 10.2337/dc16-2731

Transthyretin (TTR) is a carrier protein that transports thyroid hormones and retinol. Conventionally, a higher serum TTR level is usually taken as a sensitive clinical indicator of better protein nutritional status (1). However, emerging evidence has given us clues that TTR may contribute to gestational diabetes mellitus (GDM) (2–5). If this is the case, our previous "good impression" of TTR might be overturned. However, few population-based studies have focused on this issue.

In this prospective cohort study, we measured serum TTR, total protein (TP), albumin (Alb), and other parameter levels in the regular antenatal liver and renal function (LRF) test at 13–20 gestational weeks in 1,914 pregnant women (aged 18–45 years) belonging to the ongoing Tongji Maternal and Child Health Cohort (TMCHC) study in China. All procedures performed in studies involving human participants were in accordance with the ethical standards of the ethics review committee of Tongji Medical College of Huazhong University of Science and Technology and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Using logistic regression, we analyzed the association between TTR status (evaluated by TTR/TP and TTR/Alb) and risk of GDM based on a 75-g oral glucose tolerance test (OGTT) at 24–28 gestational weeks. Further multivariate linear regression analysis explored the relationship of TTR status to fasting blood glucose (FBG) and 1-h and 2-h postload blood glucose (PBG) in all subjects and three pre-pregnancy BMI (pre-BMI) subgroups.

Serum TTR levels ranged from 130 to 380 mg/L in our study. After adjustment for covariates, the odds ratios (ORs) of GDM, comparing highest with lowest quartile of TTR status, were 1.94 (95% CI 1.06, 3.71) for TTR/TP and 2.25 (95% CI 1.21, 4.19) for TTR/Alb (Fig. 1*A*). Further analysis after adjustment for multiple variables revealed that both TTR/TP and TTR/Alb were associated with PBG but not FBG. In all participants, TTR/TP was related to 1-h PBG ($\beta = 0.18$, $P = 0.02$) and 2-h PBG ($\beta = 0.19$, $P = 0.0006$); TTR/Alb also correlated with 1-h PBG ($\beta = 0.08$, $P = 0.048$) and 2-h PBG ($\beta = 0.12$, $P = 0.0002$). The results of the subgroup analysis are displayed in Fig. 1*B*.

Our studies found for the first time that high TTR levels (even within the upper limit of normal) were positively associated with increased risk of GDM. We also found that high serum TTR was involved in PBG upregulation rather than FBG. The results overturn our traditional understanding of TTR and indicate to clinicians that higher serum TTR not only means better nutritional status for pregnant women but also may represent a higher risk of GDM. In addition, TTR may serve as a useful indicator of GDM in the future if demonstrated in early pregnancy by more intensive studies. Our study also indicates that decreasing circulating TTR levels may be a promising therapeutic approach for the treatment of GDM in accordance with recent research (5). However, the current study only heralds the beginning of a new research direction. There are few studies focused on the association between TTR and diabetes. More human studies, especially large prospective studies with early-pregnancy women, are needed to confirm our results. Moreover, subsequent related studies should not be limited to pregnant women. The results should be

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Received 22 December 2016 and accepted 2 February 2017.

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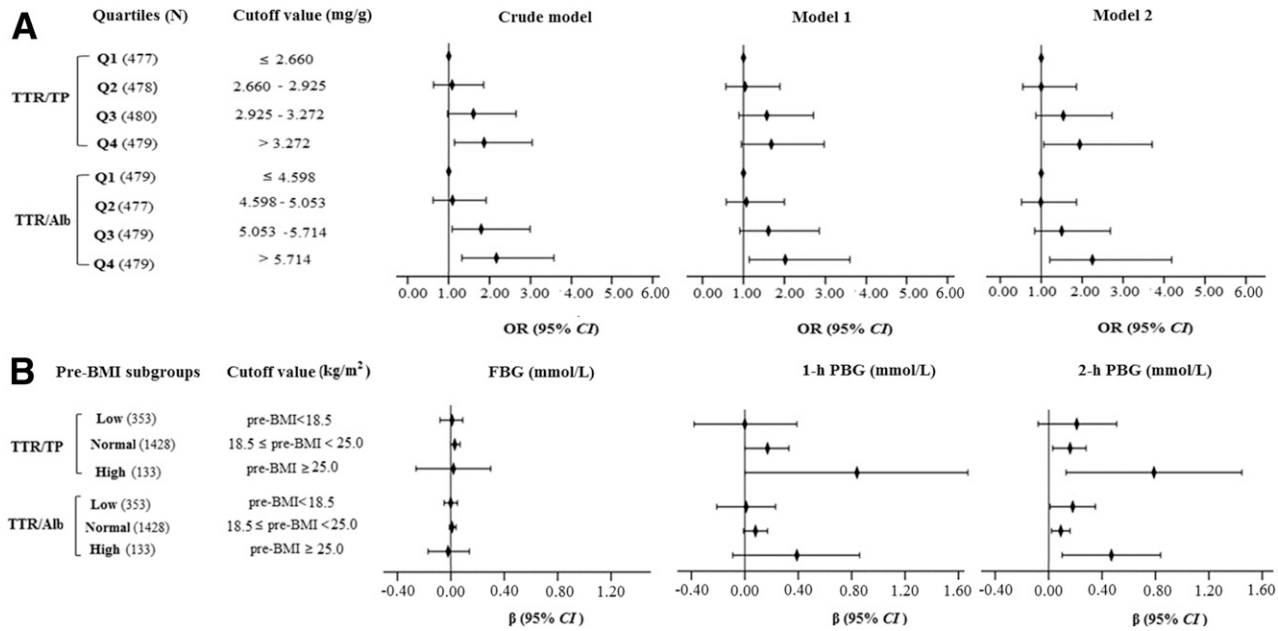

Figure 1—Logistic associations between serum TTR status and risk of GDM (*A*), and multivariate linear associations between serum TTR status and serum glucose levels in pre-BMI subgroups (*B*). In panel *A*, model 1 ORs were adjusted for BMI at LRF test, change rate of BMI from LRF test to OGTT test, and other demographic and anthropometric parameters based on the crude model; model 2 ORs were further adjusted for LRF parameters based on model 1. Panel *B* shows β values adjusted for pre-BMI, change rate of BMI from fertilization to LRF test, change rate of BMI from LRF test to OGTT, other demographic and anthropometric parameters, and LRF parameters.

validated in the general population and/or in different races. Extensive further research is also needed to explore the possible pathological mechanisms underlying the association between serum TTR and GDM as well as PBG upregulation.

Acknowledgments. The authors gratefully acknowledge the cooperation of the pregnant women who took part in this study. They also thank the staff at the maternity clinics of Hubei Maternal and Child Health Hospital and The Central Hospital of Wuhan for their considerable assistance with many aspects of this study. The authors are sincerely grateful to everyone in the Tongji Maternal and Child Health Cohort Study Group. They also thank Wei Bao (Department of Epidemiology, College of Public Health, University of Iowa) for his valuable advice and careful review of this study.

Funding. This study is supported by the National Program on Basic Research Project of China (NO.2013FY114200).

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. T.X., C.Z., X.Z., R.C., M.X., Y.W., X.H., W.W., X.L., C.L., and G.X. researched the data. T.X., C.Z., X.Z., R.C., M.X., Y.W., X.H., W.W., X.L., C.L., X.Y., and L.H. interpreted the data. T.X. drafted the manuscript. L.H. and N.Y. reviewed and edited the manuscript and contributed to discussion. N.Y. designed the study. All authors approved the final version of the manuscript. N.Y. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Richardson SJ, Cody V, Eds. *Recent Advances in Transthyretin Evolution, Structure and Biological Functions*. Berlin, Springer-Verlag, 2009
2. Refai E, Dekki N, Yang SN, et al. Transthyretin constitutes a functional component in pancreatic beta-cell stimulus-secretion coupling. Proc Natl Acad Sci U S A 2005;102:17020–17025
3. Su Y, Jono H, Misumi Y, et al. Novel function of transthyretin in pancreatic alpha cells. FEBS Lett 2012;586:4215–4222
4. Klöting N, Graham TE, Berndt J, et al. Serum retinol-binding protein is more highly expressed in visceral than in subcutaneous adipose tissue and is a marker of intra-abdominal fat mass. Cell Metab 2007;6:79–87
5. Zemany L, Bhanot S, Peroni OD, et al. Transthyretin antisense oligonucleotides lower circulating RBP4 levels and improve insulin sensitivity in obese mice. Diabetes 2015;64:1603–1614