Comparison of Multiple Cut Points for Time in Range in Relation to Risk of Abnormal Carotid Intima-Media Thickness and Diabetic Retinopathy

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Diabetes Care 2020;43:e99–e101 | https://doi.org/10.2337/dc20-0561

Compared with conventional glucose metrics including HbA_{1c}, continuous glucose monitoring (CGM) can provide more information on diabetes management. Of the multiple metrics generated by CGM, time in range (TIR) is becoming popular for assessing glycemic control in practice and research (1–3). Various target ranges for TIR have been adopted and published, with 3.9–10.0 mmol/L (70–180 mg/dL) often headlined. Since hypoglycemia accounts for a small part of time during a day, TIR is largely a metric of hyperglycemia, thus correlating with vascular complications. Logically, ideal TIR would be matched to minimal complication risk, although pragmatic considerations, namely, what is achievable, may also influence choice of level. For CGM there is a lack of information on the relationship between derived metrics and complications, but normal glucose profiles suggest very tight physiological control, with only brief postprandial excursions >140 mg/dL (7.8 mmol/L) (4,5). To begin to address the issue of the threshold of range above which vascular risk can be detected, we have investigated the associations of multiple prespecified TIR levels with carotid intima-media thickness (CIMT) and diabetic retinopathy (DR) in a large sample of people with type 2 diabetes.

Individuals with type 2 diabetes and using a stable glucose-lowering regimen for the previous 3 months were consecutively enrolled from hospitalized patients at the Department of Endocrinology and Metabolism of Shanghai Jiao Tong University Affiliated Sixth People's Hospital during April 2006–April 2012. CIMT was measured by carotid ultrasonography with a standard protocol as previously described (2). Abnormal CIMT was defined as a within-person mean CIMT ≥1.0 mm. The presence of DR was diagnosed by fundus photography with a digital nonmydriatic camera.

Each individual had 3-day masked subcutaneous glucose monitoring by a CGM system (CGMS Gold, Medtronic, Northridge, CA). TIRs were calculated as the percentage of time over 24 h between 3.9 mmol/L (70 mg/dL) and 7.8, 8.3, 8.9, 9.4, 10.0, 10.6, and 11.1 mmol/L (140, 150, 160, 170, 180, 190, and 200 mg/dL), designated $TIR_{70–140}$ through to $TIR_{70–200}$. In addition, we used time above range (TAR) obtained from the same period and with the same range of upper glucose thresholds ($TAR_{>140}$ to $TAR_{>200}$).

A binary logistic regression model was used to investigate the independent association of CGM metrics with abnormal CIMT and DR, with covariates as per Fig. 1.

In all, 2,893 people were included in the analysis. Mean ± SD age of the study population was 59.9 ± 12.0 years, 43.9% were women, and mean HbA_{1c} was 9.0 ± 2.3% (75 ± 25 mmol/mol).

The values of the TIRs with varying cut points were strongly correlated (r = 0.77–0.99, all $P < 0.001$, data not shown), and similar correlations were observed in the TARs. After adjustment for covariates including age, sex, BMI, diabetes duration, systolic blood pressure, lipids, smoking status, and the use of aspirin and statins, all TIRs and TARs were statistically significantly related to abnormal CIMT, except for $TIR_{70–140}$ ($P = 0.052$) and $TAR_{>140}$ ($P = 0.070$), and with a clear trend in odds ratio from 140 mg/dL through to 200 mg/dL (Fig. 1). The performance of prediction with various TIRs, plus conventional risk factors, did not differ significantly (C statistic = 0.732–0.735, data not shown). Similar observations can be made of DR and all TIRs and TARs (all $P < 0.001$) (Fig. 1).

Several previous studies have investigated the thresholds of glycemia for predicting vascular complications of diabetes and may shed some light on the setting of an optimal "target" range for TIR. However, CGM differs from other metrics, so it would seem that the appropriate target range can only be addressed by studies using TIR/TAR. In our study, it seems clear that cutoffs from 140 or 150 mg/dL and above are predictive,

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Received 19 March 2020 and accepted 7 May 2020

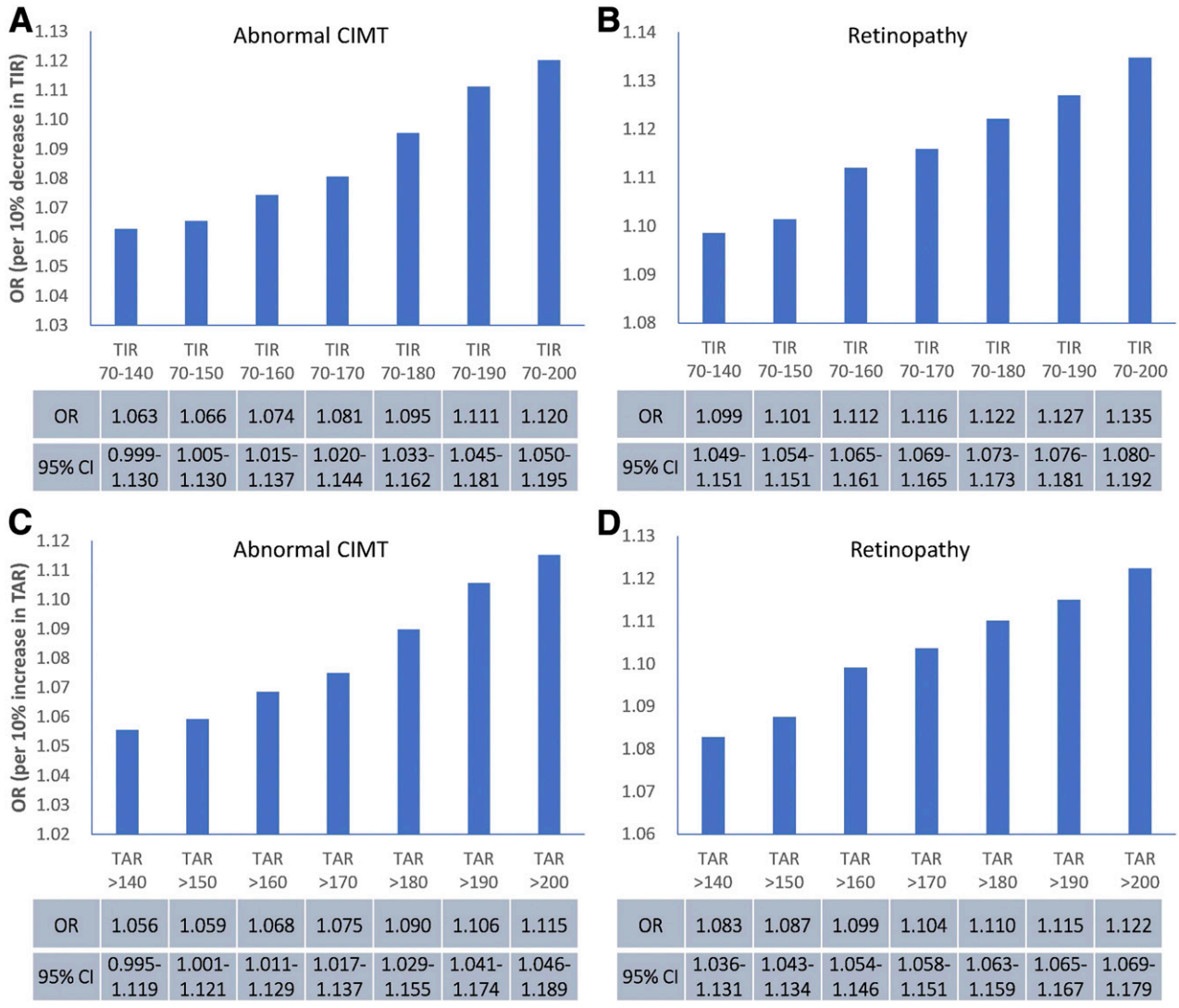

Figure 1—Odds ratios (ORs) and CIs for abnormal CIMT (*A* and *C*) and for DR (*B* and *D*) calculated by logistic regression analysis for different cut points of CGM for TIR (*A* and *B*) decrease of 10% of the day or TAR (*C* and *D*) increase of 10%. Covariates for CIMT were age, sex, BMI, diabetes duration, systolic blood pressure, triglyceride, HDL, LDL, smoking status, and the use of aspirin and statins. Covariates for DR were the same but not including statins and aspirin use.

although with increasing risk at higher glucose levels.

Several limitations of the study may be noted. This was a cross-sectional study of Chinese hospitalized patients, with only 3 days of CGM. Thus, the glucose profiles may not necessarily reflect those experienced by the patient in the longer term. Accordingly, any interpretation is hypothesis setting. Nonetheless, we note that for all four data sets the smallest differences are seen between the 140 and 150 mg/dL set points (Fig. 1), which might suggest that ongoing vascular risk has a threshold at around those levels. For TIR there is increasing risk above this level confirming that observation. We speculate that the residual risk at the cutoff of 140 mg/dL for TIR might reflect prior exposure to hyperglycemia in the years before study.

In conclusion, TIRs with the upper limit from 140–150 to 200 mg/dL (7.8–8.3 to 11.1 mmol/L) were all significantly associated with abnormal CIMT and DR. Further studies are warranted to clarify whether there are clinically meaningful differences produced by using different definitions of TIR/TAR, and which are pathogenetically significant.

Acknowledgments. The authors thank all the involved clinicians, nurses, and technicians in Shanghai Clinical Center for Diabetes for dedicating their time and skill to the completion of this study.

Funding. This work was funded by the National Key R&D Program of China (2018YFC2001004), the Shanghai Municipal Education Commission–Gaofeng Clinical Medicine Grant Support (20161430), and the Shanghai Key Clinical Center for Metabolic Disease (2017ZZ01013).

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

Author Contributions. J.L. contributed to data analysis and interpretation of data and drafted the manuscript. P.D.H. contributed to study design, interpretation of the findings, and revision of the manuscript. J.Z. contributed to study design, data analysis, and interpretation of data. J.Z. 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. Beck RW, Bergenstal RM, Riddlesworth TD, et al. Validation of time in range as an outcome

measure for diabetes clinical trials. Diabetes Care 2019;42:400–405
2. Lu J, Ma X, Shen Y, et al. Time in range is associated with carotid intima-media thickness in type 2 diabetes. Diabetes Technol Ther 2020; 22:72–78
3. Lu J, Ma X, Zhou J, et al. Association of time in range, as assessed by continuous glucose monitoring, with diabetic retinopathy in type 2 diabetes. Diabetes Care 2018;41:2370–2376
4. Shah VN, DuBose SN, Li Z, et al. Continuous glucose monitoring profiles in healthy nondiabetic participants: a multicenter prospective study. J Clin Endocrinol Metab 2019; 104:4356–4364
5. Zhou J, Li H, Ran X, et al. Reference values for continuous glucose monitoring in Chinese subjects. Diabetes Care 2009;32:1188–1193