Renin-Angiotensin System Overactivation in Type 2 Diabetes: A Risk for SARS-CoV-2 Infection?

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The novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), binds to target cells via the angiotensin-converting enzyme 2 (ACE2) receptor found in cells in blood vessels, lungs, heart, intestines, and kidneys.

Type 2 diabetes (T2D) is a risk factor for acquiring SARS-CoV-2 infection and is associated with severe disease, acute respiratory distress syndrome, and increased mortality (1). Patients with diabetes have ACE2 overexpressed in kidneys and the circulation; further, ACE2 expression may be increased in other tissues (for example, in lungs) as a consequence of angiotensin-receptor blocker (ARB) therapy (a treatment widely used for patients with diabetes), potentially increasing susceptibility to SARS-CoV-2 infection. Previously, circulatory renin-angiotensin system (RAS) activity was described in the setting of sustained hyperglycemia in diabetes (2). Here, we hypothesized that acute normalization of glycemia would modulate RAS overactivation in T2D. Therefore, plasma RAS-related protein levels were determined for T2D subjects versus control subjects at baseline and for T2D subjects after 1-h hyperinsulinemic-euglycemic clamp.

A case-control study of T2D and control subjects was approved by the Yorkshire and the Humber Research Ethics Committee, and all study participants signed an informed consent form prior to participation. The clamp was performed as detailed previously (3); all patients underwent a 10-h fast prior to the clamp, but ad libitum water ingestion was encouraged. Patients were admitted 1 h prior to the clamp procedure and remained in a supine position throughout the study. For the T2D subjects, baseline glucose was mean ± SE 7.6 ± 0.4 mmol/L (136.8 ± 7.2 mg/dL) and was reduced to 4.5 ± 0.07 mmol/L (81 ± 1.2 mg/dL) with 1-h clamp. For control subjects, glucose was maintained at 4.9 ± 0.1 mmol/L (88.2 ± 1.8 mg/dL). Slow Off-rate Modified Aptamer (SOMA)-scan plasma protein measurement (4) was used to determine RAS-related proteins: renin (REN), angiotensinogen (AGT), and ACE2. Statistical analysis was performed using GraphPad Prism 8.0. T2D ($n = 23$) and control ($n = 23$) subjects were matched for age (P = not significant [ns]); T2D subjects had higher BMI ($P = 0.0012$) and duration of disease 4.5 ± 2.9 years. Nine T2D subjects were treated with ACE inhibitor (ACEi) therapy.

In T2D subjects, total basal renin levels were elevated (1,730 ± 566 vs. 675 ± 72 relative fluorescent units [RFU], T2D vs. control, $P < 0.05$) (Fig. 1*A*), whereas angiotensinogen levels were decreased (3,786 ± 174 vs. 5,005 ± 574 RFU, T2D vs. control, $P < 0.05$) (Fig. 1*B*). ACE2 levels did not differ between T2D and control subjects (291 ± 31 vs. 281 ± 18 RFU, T2D vs. control, P = ns) (Fig. 1*C*). Acute normalization of hyperglycemia to euglycemia had no effect on levels of these RAS-related proteins (Fig. 1*A–C*).

RAS is overactivated in obesity (5), and the T2D subjects had higher BMI. To elucidate a potential relationship, T2D subjects (and control subjects) were stratified into tertiles according to BMI; however, no trends in the protein levels were seen with increasing BMI in either group. Stratification of T2D subjects into those treated or not with ACEi revealed no differences in basal RAS-related protein levels or in response to acute normalization of glycemia (ACEi vs. non-ACEi: basal AGT 4,106 ± 228 vs. 3,580 ± 235 RFU, normalized AGT 4,324 ± 275 vs. 4,125 ± 365 RFU, P = ns; basal REN 1,358 ± 258 vs. 1,969 ± 923 RFU, normalized REN 1,250 ± 207 vs. 1,903 ± 843 RFU, P = ns; basal ACE2 253 ± 10 vs. 317 ± 50 RFU,

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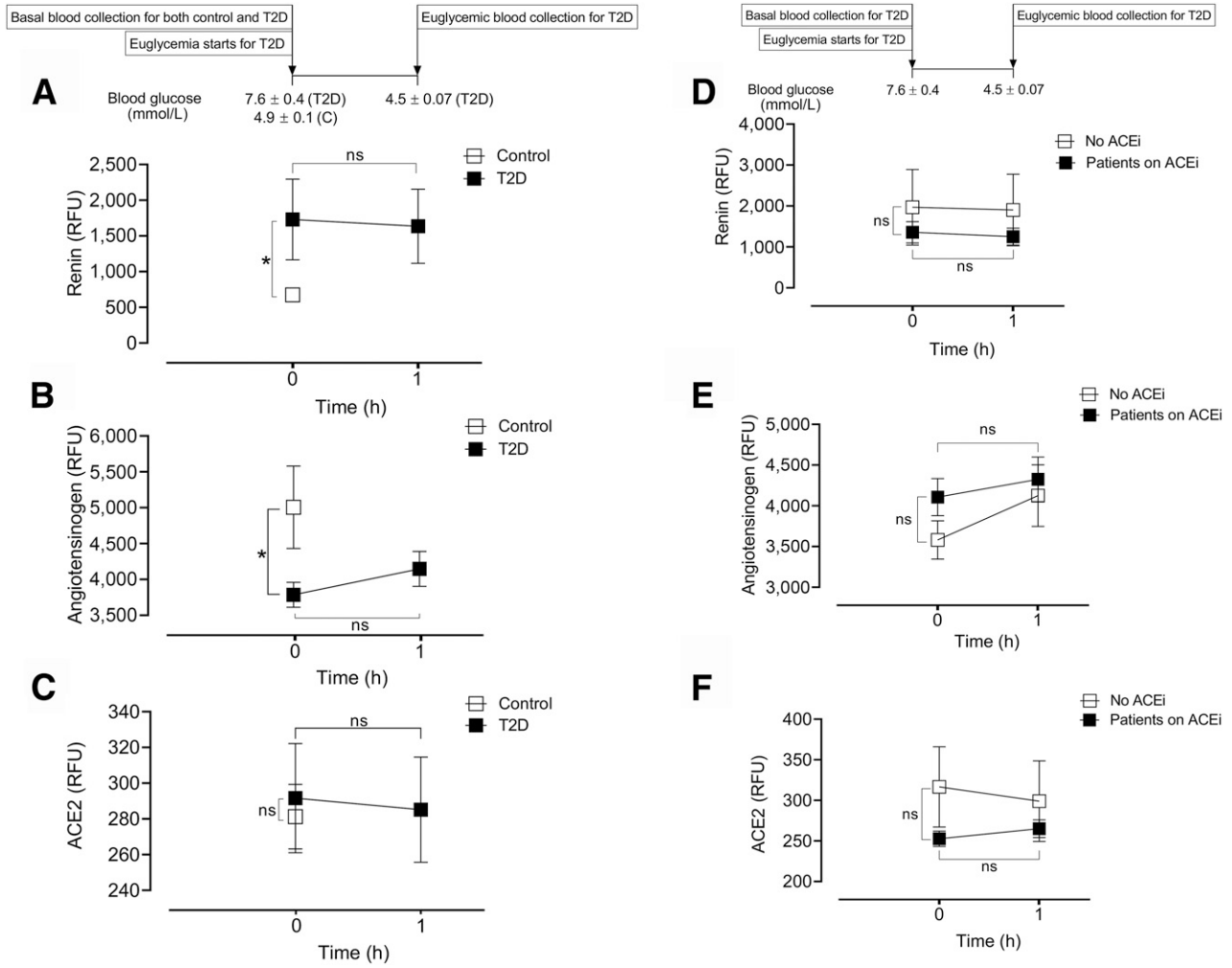

Figure 1—Circulatory levels of RAS-related proteins in T2D. *A–C*: Plasma total renin (*A*), angiotensinogen (*B*), and ACE2 (*C*) levels in control subjects (C) (open squares) and subjects with T2D (black squares). The basal level of plasma renin was higher and basal level of plasma angiotensinogen was lower in T2D subjects compared with control subjects. There was no change in the basal level of ACE2 in T2D subjects. Acute normalization of glycemia had no effect on levels of renin, angiotensinogen, or ACE2 in T2D subjects. *D–F*: Plasma levels of renin (*D*), angiotensinogen (*E*), and ACE2 (*F*) in T2D subjects who were not taking an ACEi antihypertensive drug (open squares) and in those who were taking an ACEi (black squares). There was no effect of ACEi on basal levels or acute normalization levels of RAS-related proteins in T2D subjects. $*P < 0.05$.

normalized ACE2 265 ± 11 vs. 299 ± 48 RFU, P = ns) (Fig. 1*D–F*).

Of note, plasma glucagon levels were markedly elevated in patients with T2D compared with control subjects (2,458.9 ± 291.3 vs. 1,460.8 ± 135.6 RFU of glucagon, T2D vs. control, $P < 0.01$).

This study showing elevated plasma renin, together with suppressed angiotensinogen and comparable levels of ACE2 protein, suggests RAS overactivation in T2D, independent of obesity, that was not corrected by acute normoglycemia. This suggests that immediate glucose fluctuations do not modulate RAS and are therefore unlikely to modify SARS-CoV-2 susceptibility.

Renin causes conversion of angiotensinogen to angiotensin I (ANGI); ANGI is further converted by ACE to ANGII. ACE2, by contrast, converts ANGII to ANG-1-7, a peptide beneficial in maintaining normotension. ANGII receptor blockers, such as losartan, increase ACE2 levels, whereas ACEi do not affect ACE2 levels or activity. In addition, both ACEi and ARB increased plasma renin activity, but not the plasma renin concentration, in healthy individuals and patients with hypertension, though the mechanism by which ACEi/ARB enhanced renin activity in humans has not yet been identified. However, glucagon-stimulated plasma renin activity has also been reported in humans, and we found very high basal levels of plasma glucagon in patients with T2D compared with control subjects, suggesting that the impact of ACEi therapy might be counteracted by glucagon in our study.

A limitation of this study is the measurement of plasma proteins that may not reflect tissue-level expression. In addition, we report renin concentrations rather than activity that may be discrepant in some circumstances, including underestimated renin activity in patients with liver cirrhosis and severe cardiac failure and overestimated renin activity in patients with estrogen exposure. Notably, none of these conditions were present in the patients recruited for this study, and the women were postmenopausal and not on hormone replacement therapy.

In conclusion, RAS protein levels differed between T2D and control subjects but were unaffected by glucose normalization, and no differences in plasma ACE2 levels were seen in ACEi-treated

T2D subjects. These data support the concept that discontinuing ACEi therapies in T2D subjects to reduce risk of SARS-CoV-2 infection is not beneficial.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.
Author Contributions. A.S.M.M. and A.E.B. analyzed the data and wrote the manuscript. A.A.-Q. contributed to study design; performed experiments; collected, analyzed, and interpreted data; and edited the manuscript. T.S. supervised clinical studies and edited the manuscript. S.L.A. contributed to study design, data interpretation, and the writing of the manuscript. All authors reviewed and approved the final version of the manuscript. A.E.B. 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.
Data Availability. All data for this study will be made available upon reasonable request to the corresponding author.

References

1. Zhu L, She Z-G, Cheng X, et al. Association of blood glucose control and outcomes in patients with COVID-19 and pre-existing type 2 diabetes. Cell Metab 2020;31:1068–1077.e3
2. Hollenberg NK, Stevanovic R, Agarwal A, et al. Plasma aldosterone concentration in the patient with diabetes mellitus. Kidney Int 2004;65:1435–1439
3. Al-Qaissi A, Papageorgiou M, Deshmukh H, et al. Effects of acute insulin-induced hypoglycaemia on endothelial microparticles in adults with and without type 2 diabetes. Diabetes Obes Metab 2019;21:533–540
4. Kahal H, Halama A, Aburima A, et al. Effect of induced hypoglycemia on inflammation and oxidative stress in type 2 diabetes and control subjects. Sci Rep 2020;10:4750
5. Goossens GH, Blaak EE, van Baak MA. Possible involvement of the adipose tissue renin-angiotensin system in the pathophysiology of obesity and obesity-related disorders. Obes Rev 2003;4:43–55