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RESEARCH LETTER

Acute Effects of Insulin Infusion on Kidney Hemodynamic Function in People With Type 2 Diabetes and Normal Kidney Function

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INTRODUCTION

Obesity, hyperglycemia, insulin resistance, and hyperinsulinemia are established risk factors for the development of diabetic kidney disease.[1] It is less clear, however, whether hyperinsulinemia may directly (i.e., independent of factors driving hyperinsulinemia) impair kidney function.

Animal studies suggest that hyperinsulinemia could contribute to glomerular hyperfiltration through a variety of mechanisms, including vasodilation of the afferent arteriole by increased nitric oxide levels, and attenuated tubuloglomerular feedback activity, which may result from increased proximal tubular sodium reabsorption.[2] Studies in healthy individuals show that insulin infusion increases kidney perfusion but not filtration. In people with insulin resistance and/or type 1 diabetes, insulin infusion resulted in the opposite effect, showing reductions in both filtration and perfusion, although the published data are inconsistent (Supplementary Table S1).

Considering that people with type 2 diabetes (T2D) are at high risk for hyperfiltration given the concurrent tubular hyperglycemia and have relatively severe insulin resistance, it is surprising that none of these studies investigated the effects of insulin infusion on kidney hemodynamic function in this population. In this report, we interrogate the acute effects of insulin infusion on gold standard–measured kidney hemodynamic function in people with T2D and preserved kidney function.

RESULTS

Study participants ($n = 44$) were predominantly overweight men aged 63 ± 7 years with well-controlled and metformin-treated T2D. Participants with hypertension were receiving blood pressure control medication (Table 1). During the clamp, glucose concentration was lowered to, on average, 6.1 mmol/l, and average insulin concentrations increased from 65 ± 45 to 549 ± 136 pmol/l. Systemic hemodynamic parameters were not affected by insulin infusion (Table 1).

Fasting glomerular filtration rate (GFR) and renal perfusion (RPF) were 113 ± 19 ml/min and 672 ± 138 ml/min, respectively (Figure 1). During the euglycemic-hyperinsulinemic clamp, GFR decreased to 109 ± 22 ml/min (−4 ml/min; $P = 0.005$) and RPF to 555 ± 141 ml/min (−117 ml/min; $P < 0.001$).

The reductions in GFR and RPF were accompanied by several changes in kidney hemodynamic function (Figure 1). Renal vascular resistance (+33%) was increased, accompanied by increased estimated afferent (+35%) and efferent (+15%) arteriolar resistances.

Table 1. Participant characteristics ($n = 44$)

Clinical characteristics		
Age, yr	63 ± 7	
Male, *n* (%)	34 (77)	
Current smoker, *n* (%)	4 (9)	
BMI, kg/m^2	31.1 ± 3.9	
HbA1c, %	7.4 ± 0.6	
HbA1c, mmol/mol	57 ± 7	
Diabetes duration, yr	10.2 ± 5.8	
Sodium excretion, mmol/24 h	176.0 ± 58.9	
Glucose excretion, mmol/24 h	16.8 ± 33.2	
Medication		
Metformin dose, mg	1500 (1000–2000)	
Statin use, *n* (%)	30 (70)	
Anticoagulant medication use, *n* (%)	6 (14)	
RAS inhibitor use, *n* (%)	32 (74)	
Clamp characteristics	Fasting	HE clamp
Glucose concentration, mmol/l	9.0 ± 1.5	6.1 ± 0.5
Insulin concentration, pmol/l	65 ± 45	549 ± 136
Insulin sensitivity, M value	-	3.9 ± 2.3
SBP, mm Hg	135 ± 13	145 ± 16
DBP, mm Hg	83 ± 6	84 ± 8
MAP, mm Hg	100 ± 7	105 ± 9
Heart rate, beats/min	67 ± 11	62 ± 9

BMI, body mass index; DBP, diastolic blood pressure; HbA1c, glycated hemoglobin; HE clamp, hyperinsulinemic-euglycemic clamp; M value, insulin sensitivity defined as glucose infusion rate in mg/min; MAP, mean arterial pressure; RAS, renin-angiotensin system; SBP, systolic blood pressure.
Values are expressed as mean ± SD, *n* (%), or median (IQR).

Filtration fraction (+29%) was increased, whereas estimated glomerular pressure remained unaltered (Figure 1). Fractional sodium excretion (+71%) increased during insulin infusion.

DISCUSSION

Although the strong link between hyperglycemia and diabetic kidney disease is well established, it is unclear whether elevated insulin concentrations are directly responsible for kidney damage or whether they merely reflect the underlying pathologic processes of obesity, hyperglycemia, and insulin resistance that negatively affect kidney function.[1] Given the nitric oxide–mediated vasodilatory actions of insulin, it has been proposed that hyperinsulinemia might play a direct role in the pathogenesis of glomerular hyperfiltration, a key driver of diabetic kidney disease.[2,3] Insulin infusion studies might overcome some of these difficulties in delineating the role of hyperinsulinemia on kidney hemodynamic function. In this report, we document that insulin infusion decreased both GFR and RPF by increasing preglomerular vascular resistance in people with T2D and preserved kidney function.

Experimental data revealed that insulin infusion increased GFR and RPF by causing kidney vasodilation in healthy animals, whereas the opposite effect, kidney vasoconstriction, occurred in diabetic animals (Supplementary Table S2). In humans, 7 studies investigated the effects of insulin infusion on kidney hemodynamic function in healthy individuals, of which 4 reported GFR and 5 RPF outcomes. None of the 4 studies reported a change in GFR. In contrast, 4 of the 5 studies showed an increase in RPF versus 1 study that showed no change in RPF. In people with type 1 diabetes, 3 studies reported both decreased GFR and RPF, 1 reported an increase in RPF but not GFR, and 1 documented no change in either GFR or RPF (Supplementary Table S1). These studies suggest that kidney hemodynamic function is affected by hyperinsulinemia in a direction that depends on the characteristics of the individuals studied.

It is well known that the vascular actions of insulin are reduced in obese, insulin-resistant individuals.[4] As such, Ter Maaten *et al.*[S8] showed reduced kidney vasodilatory action of insulin in insulin-resistant but otherwise healthy individuals compared with more insulin-sensitive participants (Supplementary Table S1). In support of this observation, most studies in people with recently diagnosed type 1 diabetes, who are also characterized by a degree of insulin resistance,[5] found that insulin infusion decreased, rather than increased, GFR and RPF (Supplementary Table S1).

To our knowledge, our study is the first in people with T2D to detail the acute effects of insulin infusion

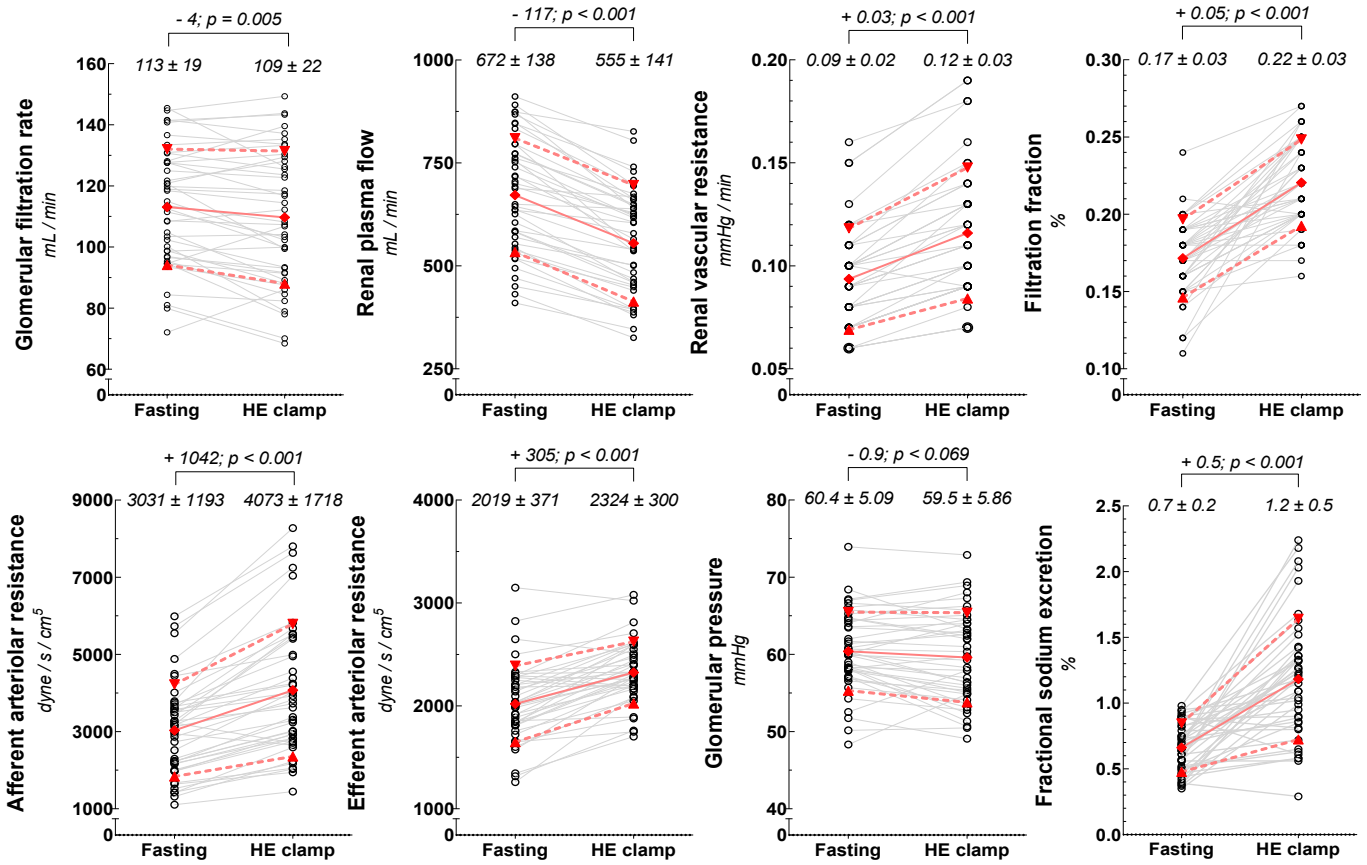

Figure 1. Effect of insulin on kidney hemodynamics in people with T2D and normal kidney function. Mean ± SD values are depicted above individual data dots and illustrated by diamonds and triangles, respectively. Arteriolar resistances and glomerular pressure were estimated by Gomez equations. HE clamp, hyperinsulinemic-euglycemic clamp.

on kidney hemodynamic function during a euglycemic-hyperinsulinemic clamp in the fasted state. It is important to note that our measurements in the fasted state are physiologically different from postprandial measurements, such as those investigated by Ruggenenti *et al.*[S10] (Supplementary Table S1). This paper showed that the effects of preprandial insulin on postprandial GFR depend on the type of insulin and the timing before the meal. It has been postulated that postprandial hyperinsulinemia could increase GFR. Kidney vasodilation due to meal ingredients, especially proteins, has also been mentioned to drive this response.[6]

We observed a reduction in GFR and RPF, which may result from increased preglomerular resistance (Figure 1). Although our population exhibited preserved kidney function, the average diabetes duration exceeded 10 years, which increases the likelihood of hyperfiltration at the single nephron level. Because insulin can induce both vasodilation and vasoconstriction, it is possible that in individuals with diabetes or those who are insulin resistant, the vasoconstrictive properties of insulin outweigh the vasodilatory properties, thereby causing kidney vasoconstriction while maintaining glomerular pressure. Protection against high glomerular pressure might even be a beneficial response that associates with preservation of kidney function.[7]

Another mechanism involved relates to kidney sodium handling. In our study, we observed higher fractional sodium excretion during insulin infusion. Although insulin is known to have a direct effect on sodium transporters in all segments of the nephron, including the proximal tubule, thick ascending limb, distal tubule, and collecting duct, and has been reported to induce sodium retention in a number of studies, the true effect of insulin on kidney sodium handling is complex, and surprisingly, human data are limited.[8] Factors such as the presence of tubular hyperglycemia and differences in regulation of sodium-glucose cotransporter systems affect tubular sodium handling. If insulin increases sodium excretion by

reducing reabsorption proximal to the macula densa, it would activate tubuloglomerular feedback, causing kidney hemodynamic changes similar to what we observed.

Our study has limitations worth discussing. We did not investigate the effects of long-term insulin infusion, which could provide different findings. However, in a recent paper, it was shown that 3-month treatment with insulin glargine reduced both GFR and RPF owing to a rise in preglomerular resistance.[9] In addition, our participants were predominantly male, were receiving metformin monotherapy, and had preserved kidney function, which limits extrapolation to other populations.

In conclusion, in people with T2D and preserved kidney function, acute insulin infusion lowered GFR and RPF and influenced kidney hemodynamic function to attenuate glomerular hypertension. These data challenge the proposed direct role of hyperinsulinemia in the development of diabetic kidney disease and warrants further study.

DISCLOSURE

PB reports serving as a consultant for AstraZeneca, Bayer, Bristol-Myers Squibb, Boehringer Ingelheim, Eli Lilly, LG Chemistry, Sanofi, Novo Nordisk, and Horizon Pharma. PB also serves on the advisory boards and/or steering committees of AstraZeneca, Bayer, Boehringer Ingelheim, Novo Nordisk, and XORTX. DHvR has acted as a consultant and received honoraria from Boehringer Ingelheim and Lilly, Merck, Novo Nordisk, Sanofi, and AstraZeneca and has received research operating funds from Boehringer Ingelheim-Lilly Diabetes Alliance, AstraZeneca, and Novo Nordisk. All honoraria are paid to his employer (Amsterdam UMC, location VUMC). DJT has received research grants from Chiesi Pharmaceutici and acts as consultant for PureIMS and Sanquin. All grants and honoraria are paid to the UMCG. All the other authors declared no competing interests.

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AUTHOR CONTRIBUTIONS

EJMvB, MN, JAJ, and DHvR designed and set up the trial. MJBvB and EJMvB were involved in sample collection and/or analysis. MJBvB performed statistical analysis. MJBvB and DHvR wrote the first draft of the paper, and the submitted version was approved by all authors.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Methods.

Supplementary References.

Table S1. Overview of human studies investigating the acute effects of insulin infusion on renal hemodynamics and kidney sodium handling.

Table S2. Overview of animal studies investigating the acute effects of insulin infusion on renal hemodynamics and kidney sodium handling.

REFERENCES

1. Tuttle KR, Agarwal R, Alpers CE, et al. Molecular mechanisms and therapeutic targets for diabetic kidney disease. *Kidney Int.* 2022;102:248–260. https://doi.org/10.1016/j.kint.2022.05.012
2. Tonneijck L, Muskiet MH, Smits MM, et al. Glomerular hyperfiltration in diabetes: mechanisms, clinical significance, and treatment. *J Am Soc Nephrol.* 2017;28:1023–1039. https://doi.org/10.1681/ASN.2016060666
3. Fluitt MB, Rizvi S, Li L, et al. Chronic insulin infusion downregulates circulating and urinary nitric oxide (NO) levels despite molecular changes in the kidney predicting greater endothelial NO synthase activity in mice. *Int J Mol Sci.* 2018;19:2880. https://doi.org/10.3390/ijms19102880
4. Muniyappa R, Montagnani M, Koh KK, Quon MJ. Cardiovascular actions of insulin. *Endocr Rev.* 2007;28:463–491. https://doi.org/10.1210/er.2007-0006
5. Bjornstad P, Snell-Bergeon JK, Nadeau KJ, Maahs DM. Insulin sensitivity and complications in type 1 diabetes: new insights.

World J Diabetes. 2015;6:8–16. https://doi.org/10.4239/wjd.v6.i1.8

6. Muskiet MHA, Tonneijck L, Smits MM, et al. GLP-1 and the kidney: from physiology to pharmacology and outcomes in diabetes. *Nat Rev Nephrol*. 2017;13:605–628. https://doi.org/10.1038/nrneph.2017.123
7. Saulnier PJ, Looker HC, Mauer M, et al. Intraglomerular dysfunction predicts kidney failure in type 2 diabetes. *Diabetes*. 2021;70:2344–2352. https://doi.org/10.2337/db21-0154
8. Brands MW, Manhiani MM. Sodium-retaining effect of insulin in diabetes. *Am J Physiol Regul Integr Comp Physiol*. 2012;303:R1101–R1109. https://doi.org/10.1152/ajpregu.00390.2012
9. Ott C, Jung S, Korn M, et al. Renal hemodynamic effects differ between antidiabetic combination strategies: randomized controlled clinical trial comparing empagliflozin/linagliptin with metformin/insulin glargine. *Cardiovasc Diabetol*. 2021;20:178. https://doi.org/10.1186/s12933-021-01358-8