Insufficient insulin administration to diabetic rats increases substrate utilization and maintains lactate production in the kidney

Good glycemic control is crucial to prevent the onset and progression of late diabetic complications, but insulin treatment often fails to achieve normalization of glycemic control to the level seen in healthy controls. In fact, recent experimental studies indicate that insufficient treatment with insulin, resulting in poor glycemic control, has an additional effect on progression of late diabetic complications, than poor glycemic control on its own. We therefore compared renal metabolic alterations during conditions of poor glycemic control with and without suboptimal insulin administration, which did not restore glycemic control, to streptozotocin (STZ)-diabetic rats using noninvasive hyperpolarized 13C-pyruvate magnetic resonance imaging (MRI) and blood oxygenation level–dependent (BOLD) 1H-MRI to determine renal metabolic flux and oxygen availability, respectively. Suboptimal insulin administration increased pyruvate utilization and metabolic flux via both anaerobic and aerobic pathways in diabetic rats even though insulin did not affect kidney oxygen availability, HbA1c, or oxidative stress. These results imply direct effects of insulin in the regulation of cellular substrate utilization and metabolic fluxes during conditions of poor glycemic control. The study demonstrates that poor glycemic control in combination with suboptimal insulin administration accelerates metabolic alterations by increasing both anaerobic and aerobic metabolism resulting in increased utilization of energy substrates. The results demonstrate the importance of tight glycemic control in insulinopenic diabetes, and that insulin, when administered insufficiently, adds an additional burden on top of poor glycemic control.