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Interference of urinary albumin-to-creatinine ratio measurement by glycosuria: clinical implications when using SGLT-2 inhibitors

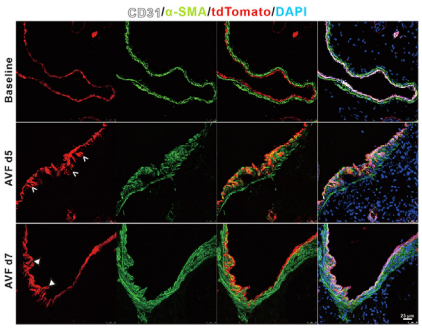
The Jaffe reaction is the most commonly used test to measure creatinine levels. High levels of glucose can interfere with Jaffe, causing it to overestimate creatinine. Because the use of sodium-glucose cotransporter 2 (SGLT2) inhibitors (SGLT2i) is increasing dramatically in patients with chronic kidney disease, Chapman *et al.* studied whether the glycosuria seen with SGLT2i affects urine creatinine measurement. They found that increasing concentrations of urine glucose, within the range commonly induced by SGLT2 inhibition, did increase urine creatinine, especially in more dilute samples. This will lower the measured urine albumin-to-creatinine ratio. Although the effect size was small, the therapeutic response to SGLT2i is assessed, in part, by changes in proteinuria. Such results may, therefore, be misleading. However, enzymatic assays for creatinine are not affected by glucose. It will be important to report the assay used to measure creatinine in future studies. **See page 787**

Post hoc analysis of SUSTAIN 6 and PIONEER 6 trials suggests that people with type 2 diabetes at high cardiovascular risk treated with semaglutide experience more stable kidney function compared with placebo

The glucagon like peptide-1 (GLP-1) receptor agonists reduce albuminuria in patients with type 2 diabetes. GLP-1 agonists also seem to stabilize kidney function. To look specifically at glomerular filtration rate, Tuttle *et al.* performed a *post hoc* analysis of 2 large trials of the GLP-1 agonist semaglutide in patients with type 2 diabetes at high risk for cardiovascular events. Over 6000 patients were studied. The semaglutide arm had a significantly lower negative estimated glomerular filtration rate (eGFR) slope than the placebo-treated patients, suggesting a slower decline in kidney function. Furthermore, the hazard ratios of time to a fixed decrease in eGFR between 30% and 57% favored semaglutide. Although the beneficial effects of semaglutide were not significantly different when patients were stratified by baseline eGFR, the largest effects were seen in the group with baseline eGFR between 30 and 60 ml/min per 1.73 m^2. These data suggest that another anti-diabetic drug can stabilize kidney function in patients with chronic kidney disease. **See page 772**

Osteopontin mediation of disturbed flow–induced endothelial mesenchymal transition through CD44 is a novel mechanism of neointimal hyperplasia in arteriovenous fistulae for hemodialysis access

Human arteriovenous fistulae (AVF) used for dialysis access often develop neointimal hyperplasia in areas of chaotic blood flow, leading to access dysfunction. Using a rodent aortocaval fistula model, Chang *et al.* found that in areas of disturbed blood flow, especially at the arteriovenous anastomosis, both endothelial cells and smooth muscle cells were present, suggesting induction of endothelial-to-mesenchymal transition (EMT). Lineage tracing showed endothelial cells contributed to about 25% of the neointima. Osteopontin and CD44 were also present in the lumen in areas of disturbed flow; and in human umbilical vein endothelial cells, osteopontin induced EMT, which could be attenuated by knocking down CD44. EMT was also attenuated in AVF created in CD44 knockout mice. Importantly, osteopontin and CD44 were also found in AVF of patients, suggesting that interventions in this pathway may be useful to treat neointimal hyperplasia in dialysis accesses. **See page 702**



Reduction of anaerobic glycolysis contributes to angiotensin II-induced podocyte injury with foot process effacement

Activation of the renin-angiotensin system results in podocyte injury indirectly through increasing glomerular pressure and directly through actions of angiotensin II on podocytes. Chen *et al.* postulated this may be due to altered podocyte metabolism, leading to a decrease in the energy needed to maintain podocyte form and function. Exposure of podocytes to angiotensin II either *in vitro* or *in vivo* decreased glycolysis, possibly through reduction in the expression of pyruvate kinase M2, a critical glycolytic pathway enzyme. Inhibition of glycolysis was accompanied by adenosine triphosphate deficiency and podocyte cytoskeletal remodeling and apoptosis. Consistently, podocyte pyruvate kinase M2 expression was reduced in patients with hypertensive nephropathy and diabetic kidney disease. These investigators suggest that activation of glycolysis may be a possible therapeutic intervention for the treatment of podocyte injury. **See page 735**