Type 2 diabetes (T2D)-related vascular dysfunction and hemorheological abnormalities could possibly be amplified by sickle cell trait (SCT). These alterations could potentially increase the risk of vascular complications in individuals with combined T2D and SCT. Therefore, this study used a mouse model to determine whether vascular function and blood rheology were more severely altered in combined T2D and SCT than in T2D or SCT alone. Methods: Townes transgenic mice with or without SCT received a 12-week high fat high sucrose or standard diet to create models of combined T2D-SCT, T2D, SCT, and controls. Pressure-induced vasodilation (PIV) and sodium nitroprusside (SNP)-mediated vasodilation in-vivo, and hemorheological parameters were measured. Results: No significant differences in blood viscosity, hematocrit, erythrocyte deformability, or PIV were observed between the control and T2D mice, or the control and SCT mice. However, blood viscosity, erythrocyte deformability, and PIV were significantly altered in the T2D-SCT mice compared to the control mice. There were no differences in SNP response between the groups. Conclusions: Although neither T2D or SCT alone had significant effects on blood rheology parameters or vascular function, combined T2D-SCT mice had significantly altered blood rheology and significantly impaired vascular function.