**Introduction:** Podocyte responses can be disrupted in diabetes/diabetic nephropathy leading to podocyte damage and kidney dysfunction. PTP1B is a protein tyrosine phosphatase that can dephosphorylate and inactivate the insulin receptor and a therapeutic target for diabetes. PTP1B inhibition or knockout in podocytes, has been shown to have beneficial effects in experimental models of diabetic nephropathy. Whether this is the case in clinical nephropathy and whether effects are only due to improvements in insulin signalling is unclear. The objective was to determine if a clinical PTP1B inhibitor, trodusquemine could reverse the effect of high glucose-induced insults on human podocyte function.

**Methods:** Conditionally immortalised, insulin resistant human podocytes were exposed to insulin (100nM) for 15 minutes or high glucose (30mM) for 72hr in the presence or absence of trodusquemine. Effects of trodusquemine on the expression of glucose sensing, structural and (ECM) proteins, and inflammatory responses that are altered in diabetic nephropathy, were determined by Western blotting.

**Results:** Human conditionally immortalised podocytes showed resistance to insulin signalling. Trodusquemine significantly increased phospho-Akt levels both basally and in response to insulin, suggesting this was independent of insulin receptor signalling. These insulin-resistant human podocytes exhibited high glucose-mediated down-regulation of AMPK. Exposure of podocytes to high glucose decreased the expression of podocin, a filtration slit protein and increased expression of the ECM protein, fibronectin. Trodusquemine treatment reversed these deleterious, high glucose-induced effects, independently of insulin receptor mediated signalling. As expected, podocyte treatment with LPS, which mimicked inflammatory conditions, resulted in JNK activation, an effect reversed by Trodusquemine treatment.

**Conclusion:** We present evidence that pharmacological inhibition of PTP1B, in addition to its already well described direct actions on insulin signalling, results in insulin receptor independent effects that can reverse the pathogenic effects of high glucose and LPS on human podocytes. These studies provide the first evidence that clinical PTP1B inhibitors are likely to have beneficial effects in diabetic nephropathy due to insulin receptor dependent and independent effects that can preserve human podocyte function.