

Background

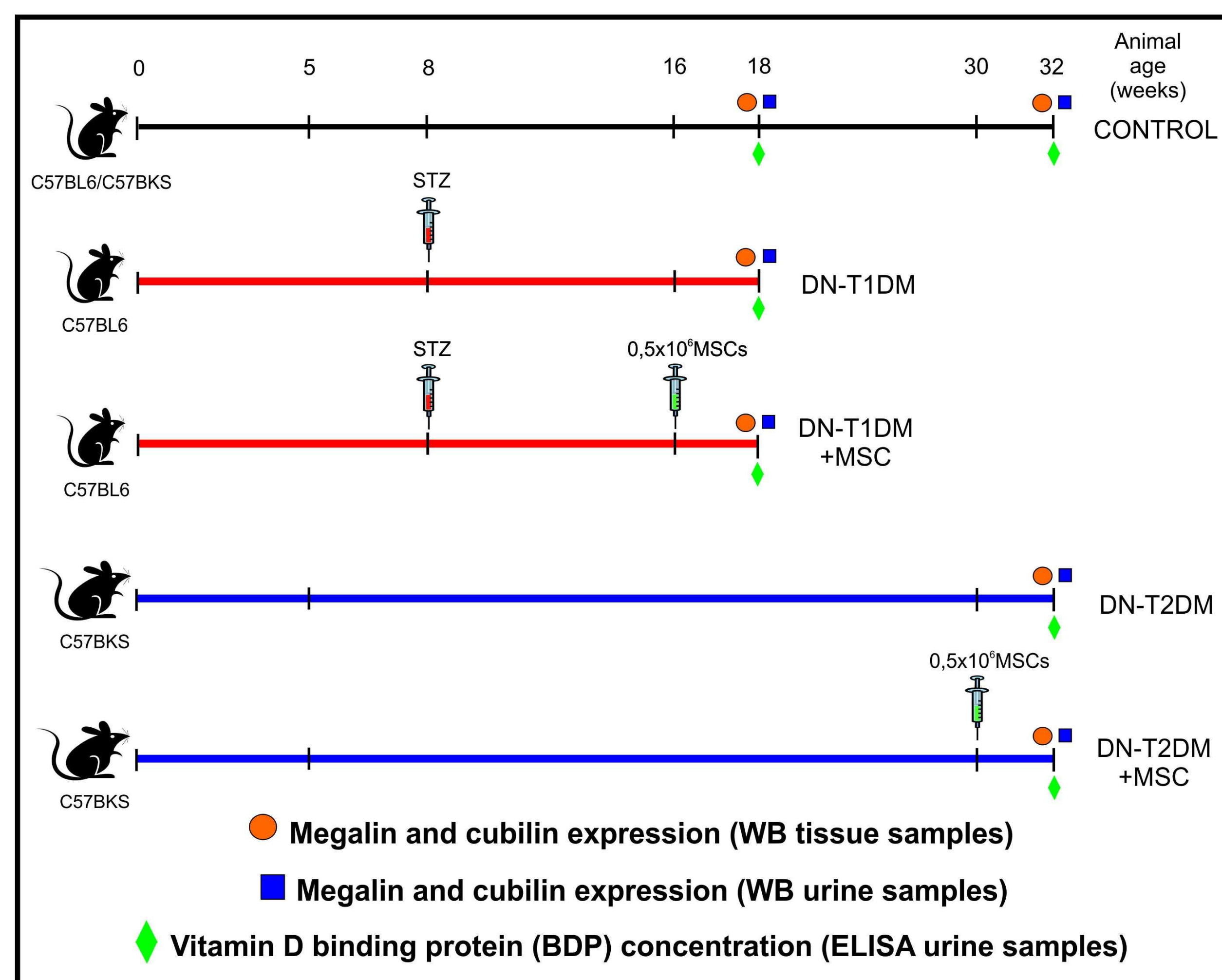
Megalin and cubilin are membrane endocytic receptors that interact for endocytosis of a vast variety of filtered plasma proteins in kidney proximal tubule cells. One characteristic of diabetic nephropathy is the increase of albumin filtration and the inhibition of megalin and cubilin mediated albumin endocytosis, leading to increased albuminuria.

Objective

The objective of our work was to study the influence of mesenchymal stem cells (MSC) therapy on tubular protein transporters in kidney of type 1 and type 2 diabetic animals.

Materials & Methods

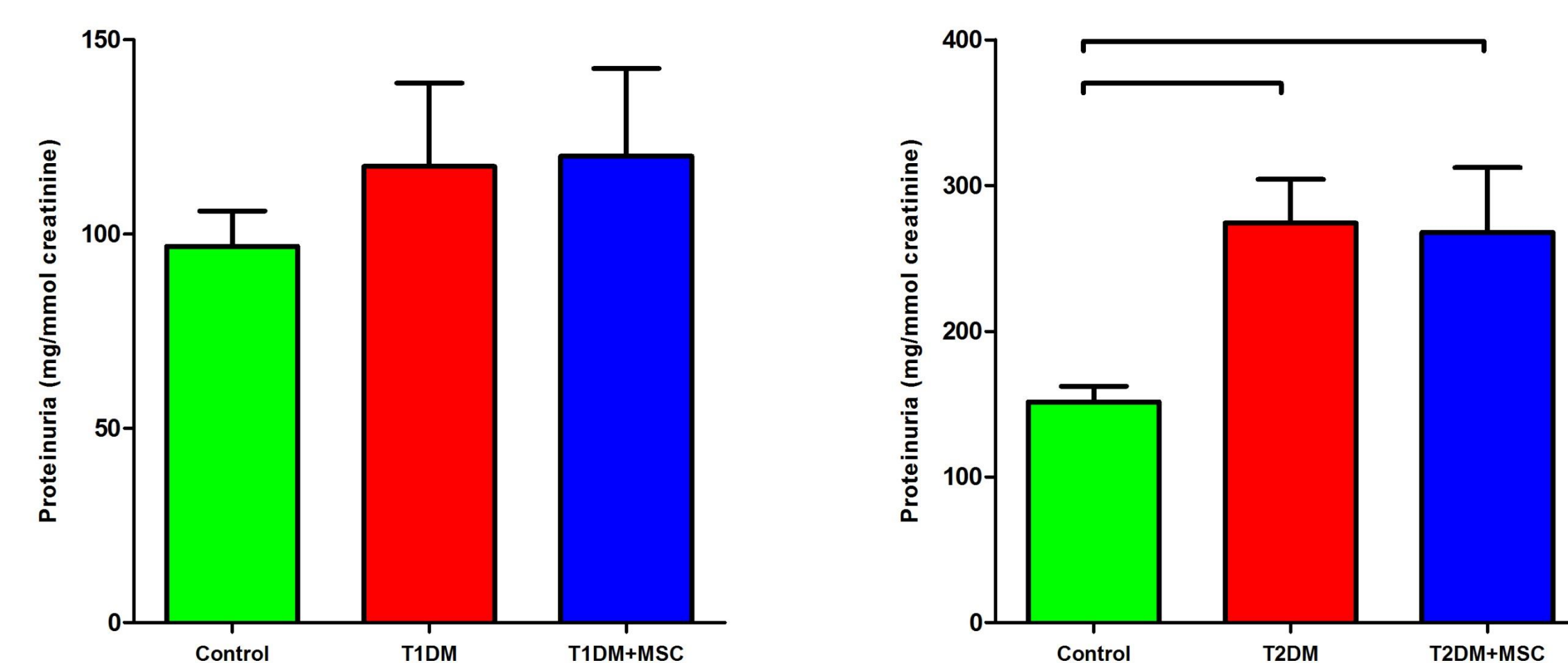
C57BL/6 and C57BKS mice (Jackson Laboratory) were housed at constant temperature and humidity, with a 12:12 hours light-dark cycle and unrestricted access to a standard diet and water. **Type 1 diabetic mice:** Eight week-old male C57BL/6 mice were lightly anesthetized. Streptozotocin was dissolved in vehicle A (0.1 M citrate buffer, pH 4.5), and immediately injected intraperitoneally at a dose of 200 mg/kg/day. **Type 2 diabetic mice:** C57BKS (db/db) and normal heterozygote controls (db/+) from Jackson Laboratories, about 30 weeks-old were used. MSCs (0.5×10^6), labeled with 8 mg/mL Dil (Invitrogen, Eugene, OR) were resuspended in 0.2 mL of 5% mice plasma and administered via tail vein to lightly anesthetized mice at eighteen (T1DM) and thirty (T2DM) weeks-old. We studied by Western Blot the expression of both membrane endocytic receptors, megalin (tissue samples) and cubilin (tissue and urine samples). Furthermore, we explored the functionality of megalin by the quantification of vitamin D-binding protein (BDP, urine) by ELISA method.



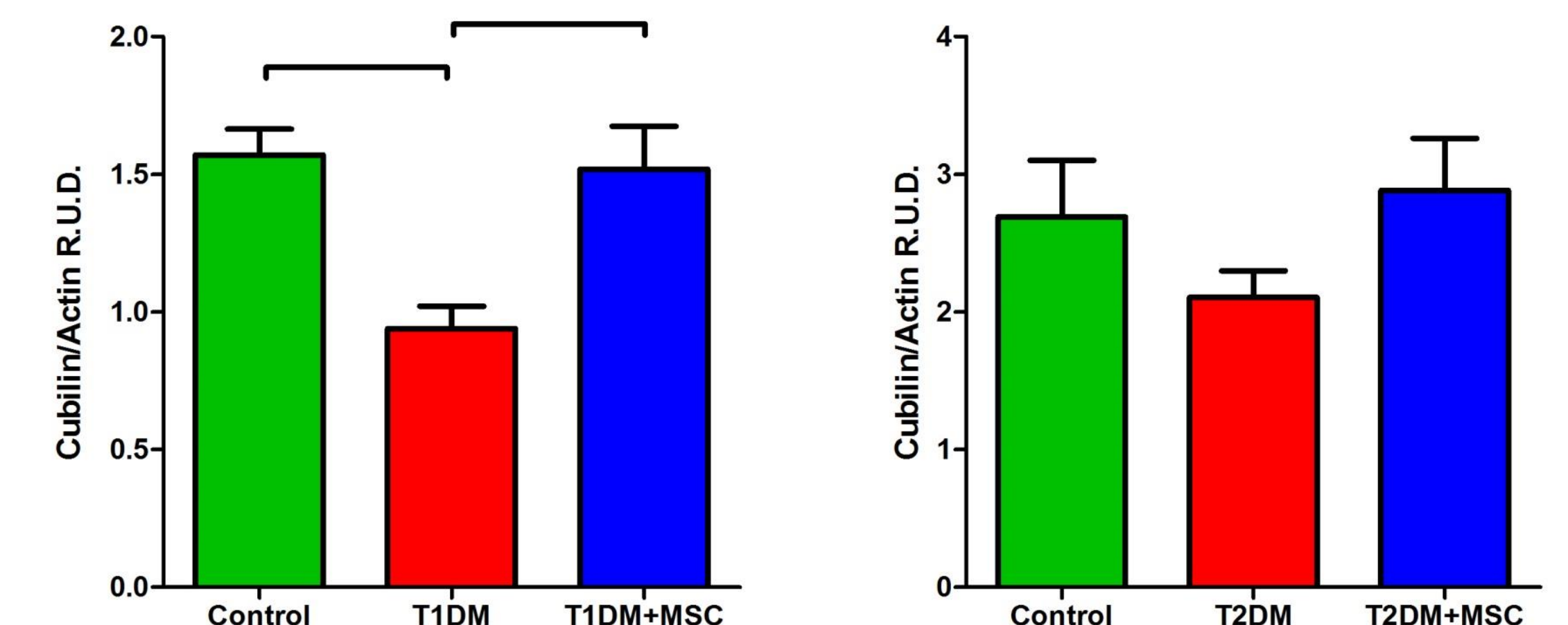
Results

The expression of megalin and cubilin decreases in T1 diabetic animals and after 2 weeks of MSC administration the expression increases. In T2 diabetic animals, only megalin decreases significantly its expression and treatment does not increase levels. Proteinuria and BDP concentration are increased in both diabetic models, but only BDP levels decrease in T2 animals after MSC administration. Finally, levels of cubilin in urinary samples are increased in both diabetic models and only decrease significantly in T1 diabetic animals that received the cell therapy.

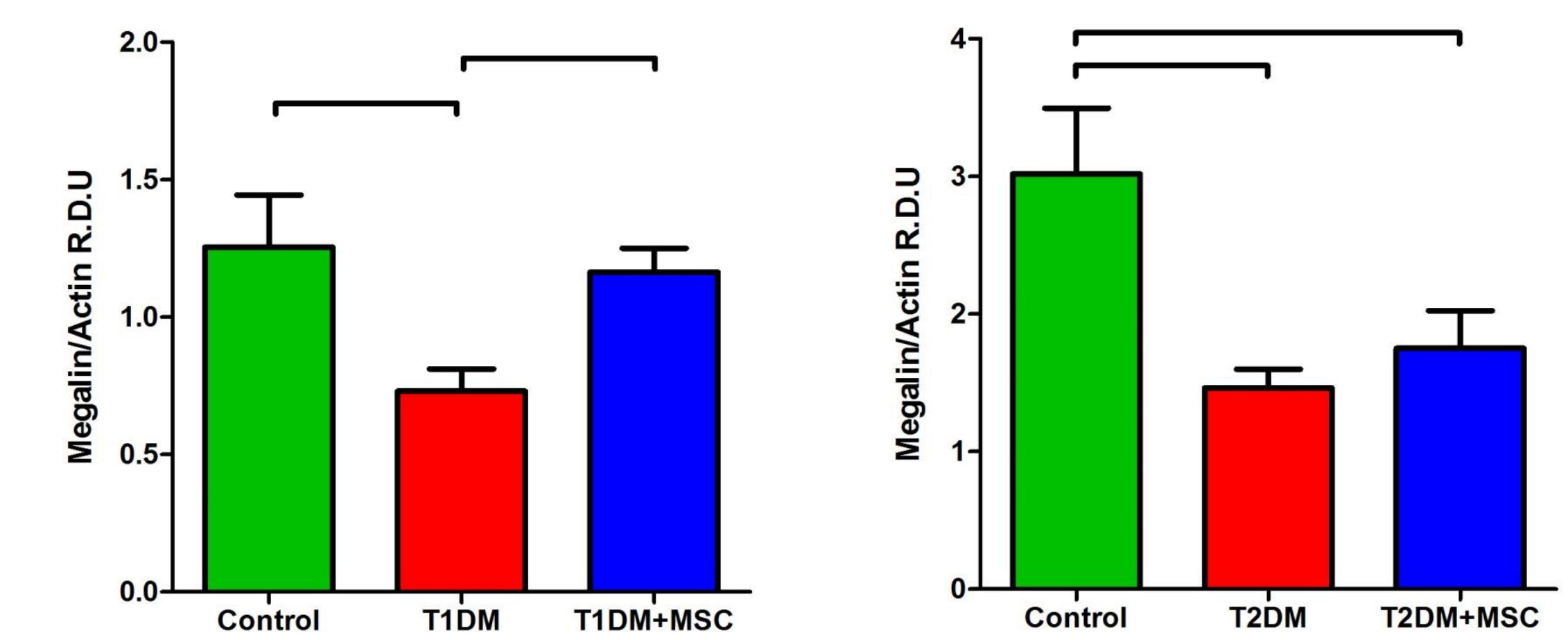
Proteinuria



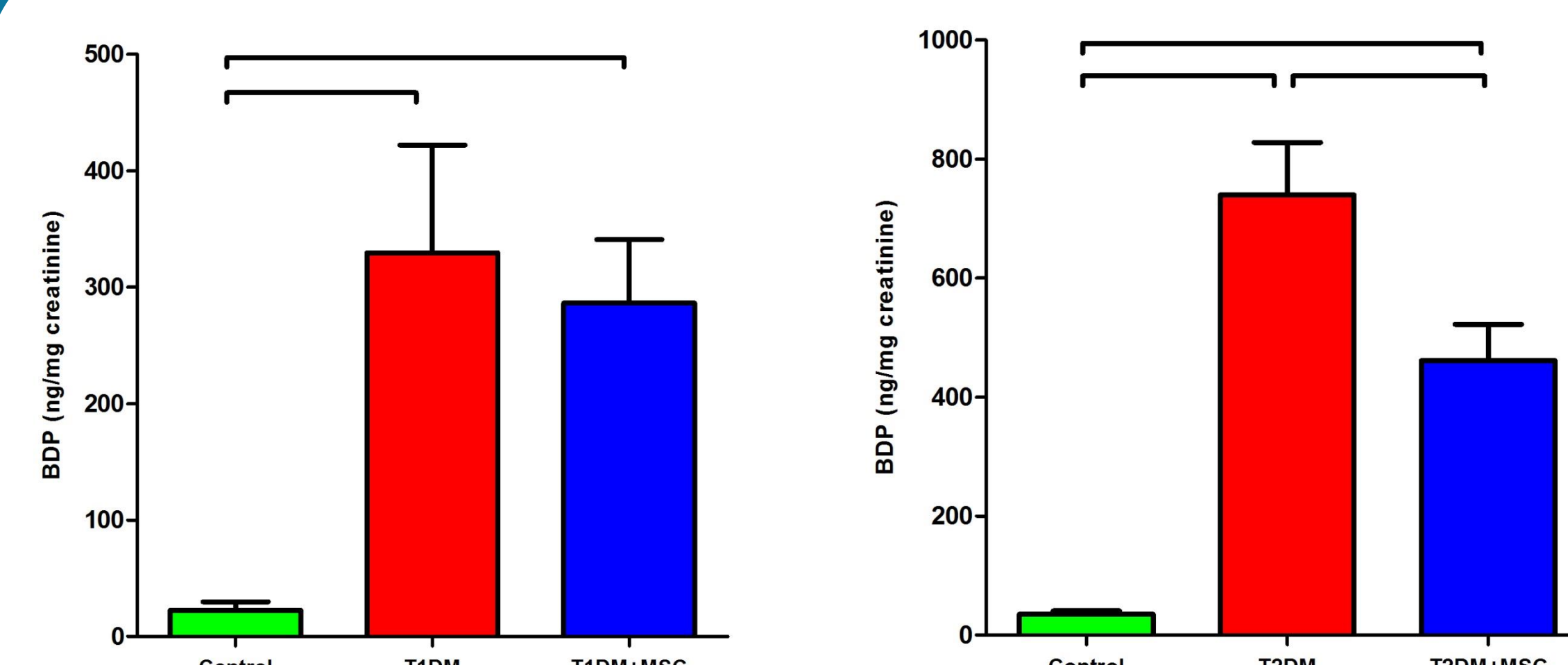
Tissue cubilin



Tissue megalin



Urine BDP



Urine cubilin

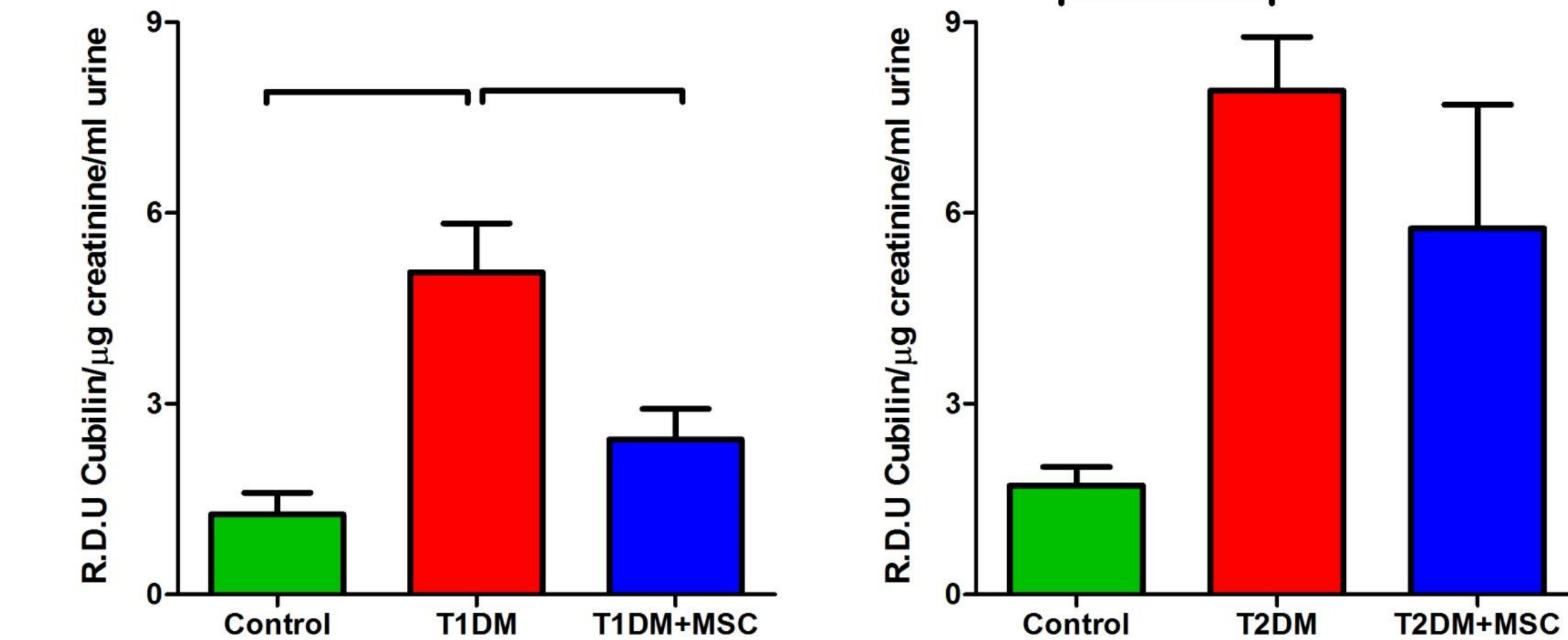


Figure legends: Proteinuria, urine vitamin D binding protein (BDP), megalin (tissue) and cubilin (tissue and urine) determinations in control, type 1 (T1DM) and type 2 (T2DM) diabetic animals and T1DM and T2DM animals that receive mesenchymal stem cell (MSC) treatment. N= 6 per group. Bars indicate significant differences between groups (One way ANOVA, Tukey's tests).

Conclusions

MSC administration in both experimental diabetic models improves the action of tubular protein transporters, however its potential role as a therapy and the physiopathologic mechanisms involved are currently under study.



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