MAXACALCITOL EXERTS ITS RENOPROTECTIVE EFFECTS IN NON-OBESE TYPE 2 DIABETIC RATS VIA SUPPRESSION OF OXIDATIVE STRESS AND AMELIORATION OF THE NRF2-KEAP1 PATHWAY

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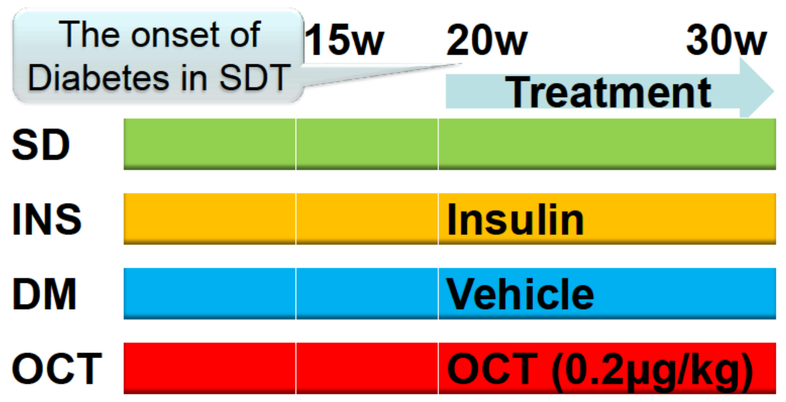
OBJECTIVES

- Diabetes mellitus is a major cause of end-stage kidney disease, which involves many complex factors and complications.
- Oxidative stress is one of the important risk factors in the progression of diabetic nephropathy.
- Serum vitamin D levels are associated with the all-cause and CVD mortality.
- Although it is suggested that vitamin D could suppress oxidative stress, the detailed mechanism remains unknown.
- The aim of our study was to ascertain whether vitamin D could attenuate oxidative stress and prevent the progression of diabetic nephropathy.

METHODS

The Spontaneously Diabetic Torii (SDT) rat, a non-obese type 2 diabetic model, were divided into the three treatment groups. We used the SD rats for reference and the insulin-treated group as control.



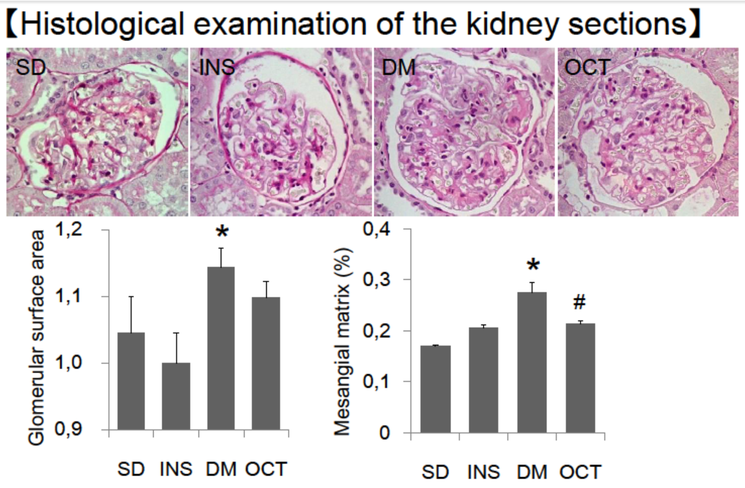
【Characteristics of SD and SDT rats】

	SD	INS	DM	OCT
BW (g)	714.6 ± 14.2	581.4 ± 14.3	448.0 ± 11.0*	464.4 ± 6.4*
Kidney /BW (mg/g)	2.57 ± 0.02	3.94 ± 0.08	6.33 ± 0.41*	5.96 ± 0.11*
SBP (mmHg)	129 ± 4	134 ± 3	142 ± 3	139 ± 4
UAE (mg/24hr)	0.19 ± 0.08	9.70 ± 2.41	77.82 ± 11.83*	38.42 ± 3.53#
Ccr/BSA (ml/min/m^2)	0.95 ± 0.21	0.93 ± 0.12	1.30 ± 0.27	1.32 ± 0.12
HbA1c (%)	3.2 ± 0.1	6.4 ± 0.6	12.1 ± 0.3*	11.0 ± 0.2*
Albumin (g/dL)	4.0 ± 0.2	3.6 ± 0.2	3.5 ± 0.2	3.3 ± 0.2
Calcium (mg/dL)	11.5 ± 0.4	10.7 ± 0.4	10.9 ± 0.6	10.8 ± 0.3
Phosphorus (mg/dL)	8.4 ± 0.5	8.3 ± 0.9	8.6 ± 0.6	9.0 ± 0.6
PTH (pg/mL)	201.1 ± 36.0	133.1 ± 54.7	130.8 ± 67.7	40.4 ± 12.5

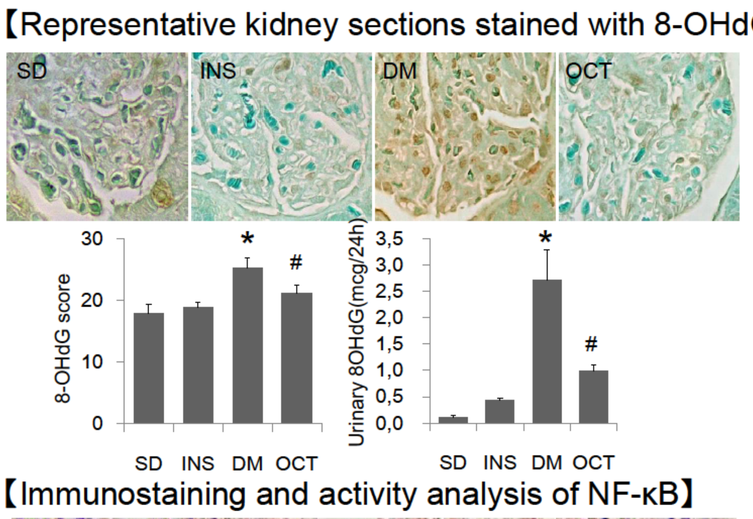
Values are mean ± SEM. *, $P < 0.05$ vs. INS; #, $P < 0.05$ vs. DM

RESULTS

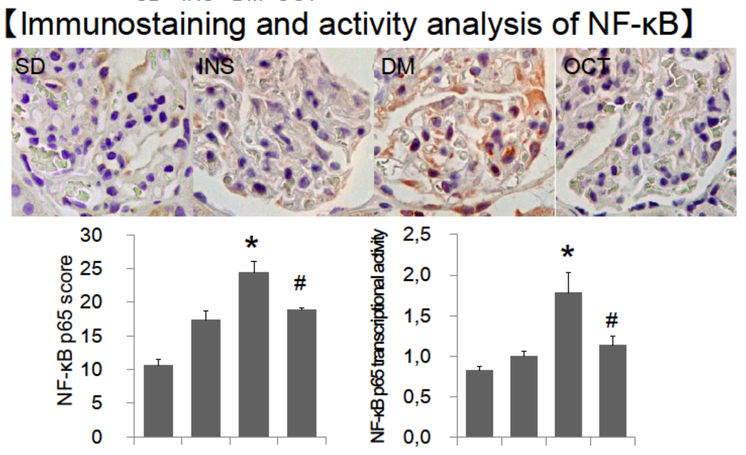
【Histological examination of the kidney sections】



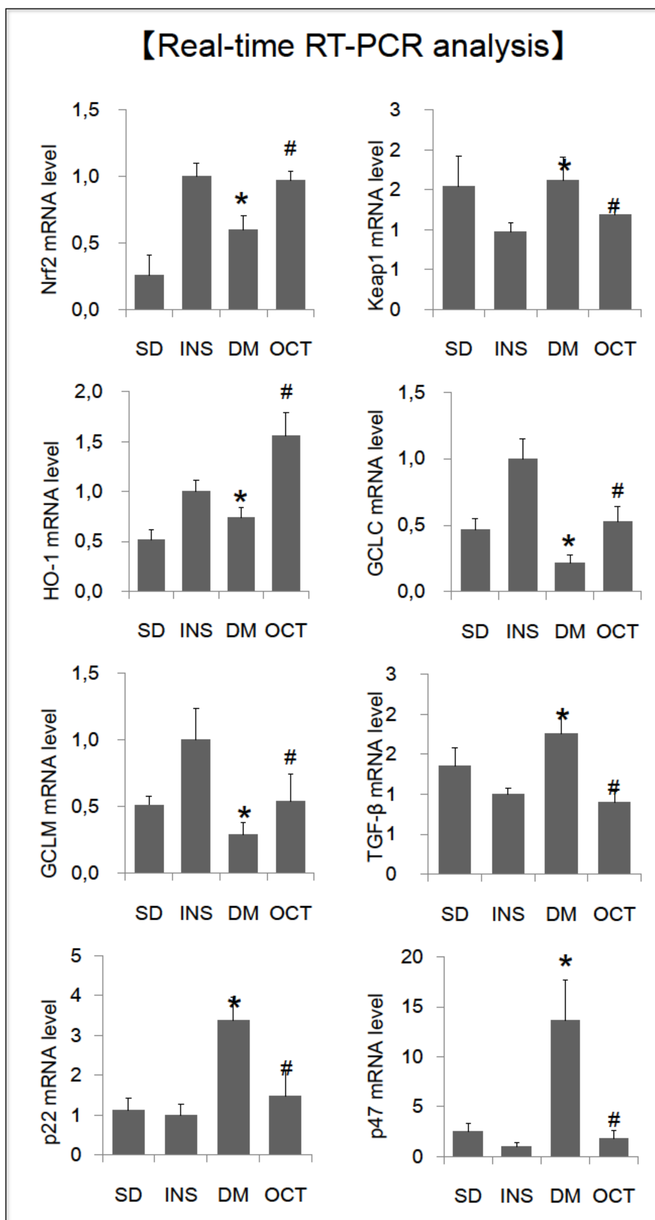
【Representative kidney sections stained with 8-OHdG】



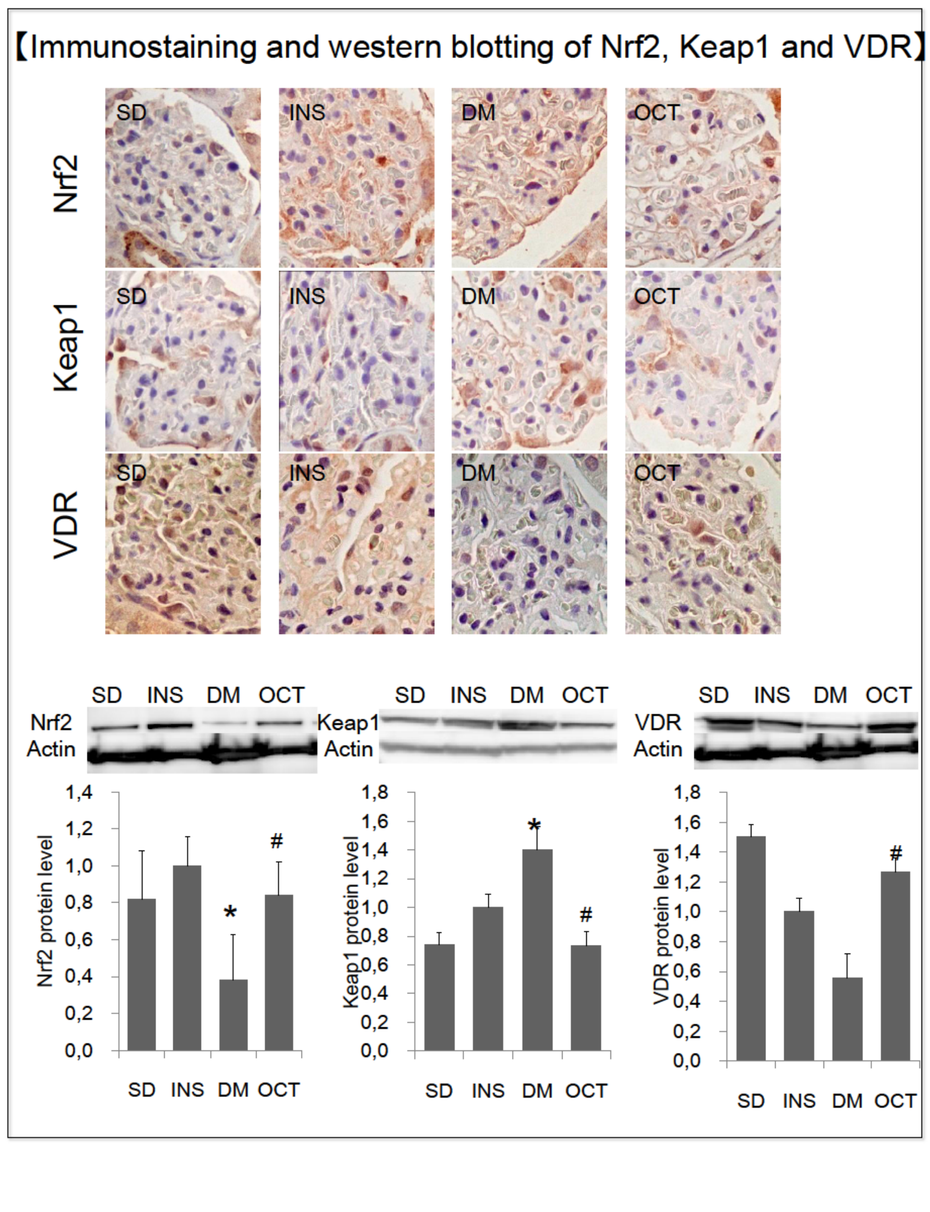
【Immunostaining and activity analysis of NF-κB】



【Real-time RT-PCR analysis】



【Immunostaining and western blotting of Nrf2, Keap1 and VDR】



CONCLUSIONS

- Urinary excretion of albumin and expansion of mesangial matrix increased in the DM group, whereas OCT treatment ameliorated these abnormalities.
- OCT improved urinary excretion and immunohistochemical score of 8-OHdG and mRNA expression of NADPH oxidase.
- The expressions of Nrf2 and its downstream genes were decreased and the expression of Keap1 increased in the DM group; however, these were restored in DM+OCT group.
- **The results of present study suggest that OCT attenuates the progression of diabetic nephropathy by suppression of oxidative stress and amelioration of the Nrf2-Keap1 pathway in non-obese type 2 diabetes.**

REFERENCES:

Fujii H, Kono K, Nakai K, Goto S, Komaba H, Hamada Y, Shinohara M, Kitazawa R, Kitazawa S, Fukagawa M: Oxidative and nitrosative stress and progression of diabetic nephropathy in type 2 diabetes. Am J Nephrol 2010; 31: 342-52.