Vitamin D receptor activator Maxacalcitol prevents the progression of diabetic cardiomyopathy independently of renin-angiotensin system inhibition

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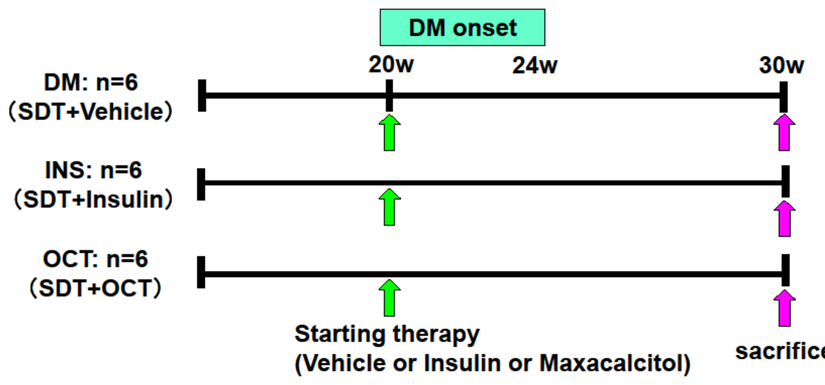
Background/Aims

- Diabetes mellitus (DM) is an important risk factor for chronic kidney disease (CKD) and cardiovascular disease (CVD).
- Recent reports showed the significant association between vitamin D and CVD events and mortality.
- It has been also known that decreased vitamin D is associated with the pathogenesis of DM.
- Maxacalcitol (OCT) is a vitamin D receptor activator that decreases serum parathyroid hormone levels in patients with CKD.
- Recently, it has been reported that OCT does not reduces renin-angiotensin system (RAS) activity significantly.
- In this study, we investigated the effect of OCT on cardiac damage and RAS in DM.

Methods

In the present study, we used SDT rats, which are non-obese type 2 diabetes model rats. At 20 weeks, these were divided into three groups: vehicle-treated SDT rats (DM, N=6), insulin-treated SDT rats (INS, N=6), and maxacalcitol-treated SDT rats (OCT, N=6). At 30 weeks, the rats were sacrificed and urinary and blood biochemical analysis and cardiac histological analysis were performed in these groups. (study ①)

【Study ① protocol】



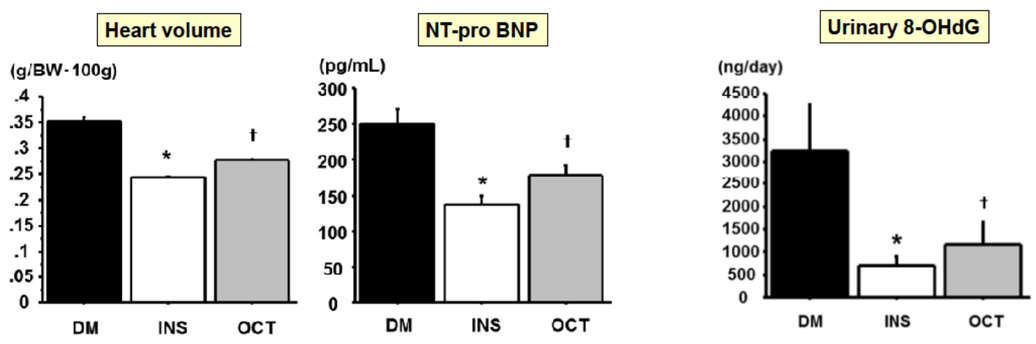
To evaluate the effect of OCT on RAS, we performed a further study using aliskiren, which is a direct renin inhibitor. SDT rats were divided into two groups: aliskiren-treated group (AL, N=6) and aliskiren plus OCT-treated group (AL+OCT, N=6) and evaluated RAS and cardiac change. (study ②)

Results

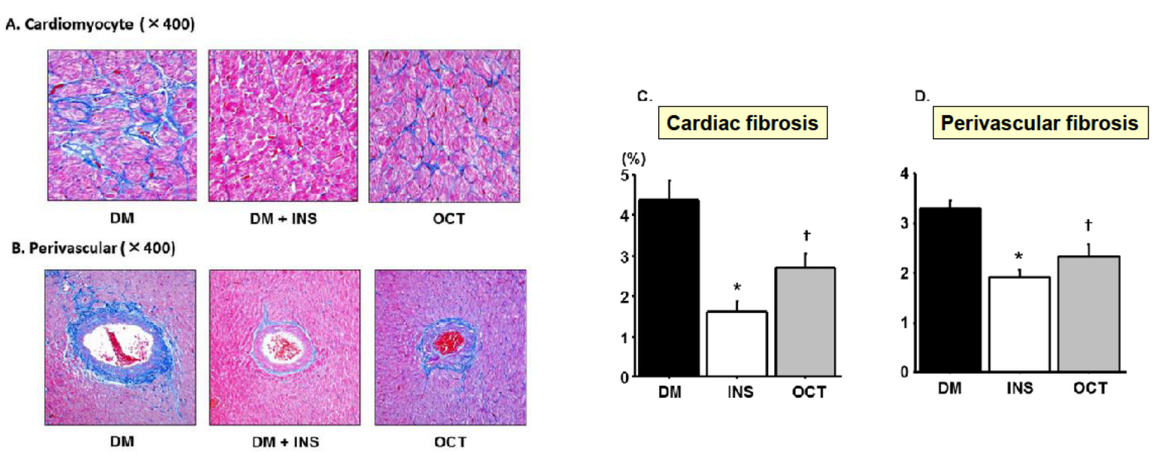
【Animal characteristics at 30 weeks】

	DM	INS	OCT
Body weight (g)	437.9±6.6	576.9±10.2 *#	452.8±5.4
Blood pressure (mmHg)	145.7±1.2	136.6±1.7 *	143.2±2.0
Ccr (ml/min/)	9.7±0.5	7.2±0.6	9.0±1.3
TP (mg/dL)	5.6±0.1	6.3±0.1 *#	5.6±0.1
Alb (mg/dL)	3.4±0.1	3.6±0.1 #	3.3±0.1
HbA1c (%)	11.3±0.1	4.7±0.5 *#	10.9±0.1
U-Alb (mg/day)	74.3±7.7	14.6±1.7 *#	36.6±2.7 †

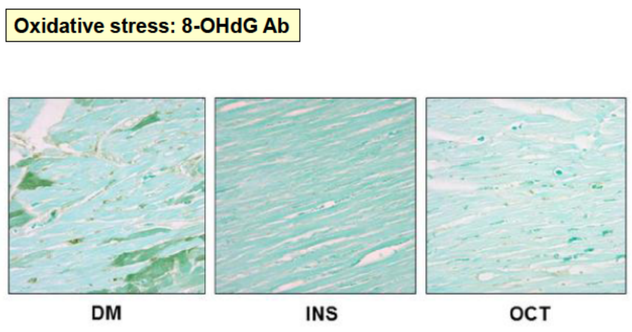
*; DM v.s INS, $p<0.05$, #; OCT v.s INS, $p<0.05$, †; DM v.s OCT, $p<0.05$



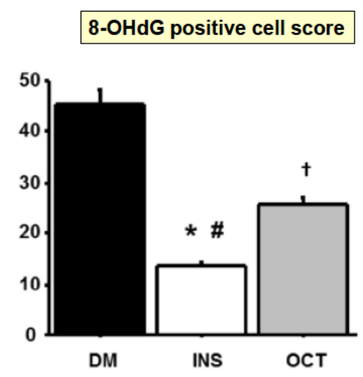
【Evaluation of cardiac histology at 30 weeks】



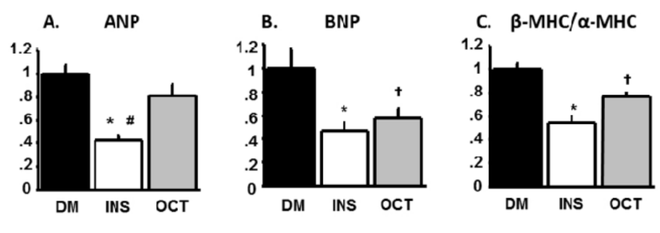
Oxidative stress: 8-OHdG Ab



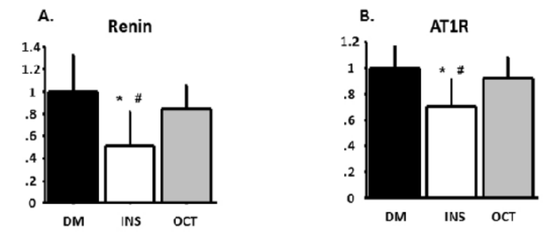
8-OHdG positive cell score



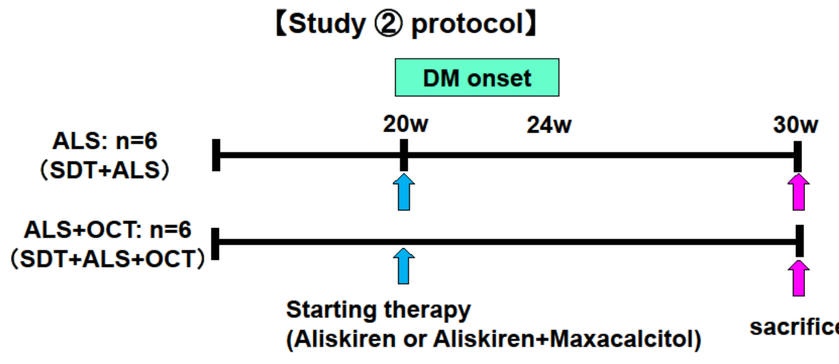
【mRNA expression of cardiac hypertrophy-related genes: study ①】



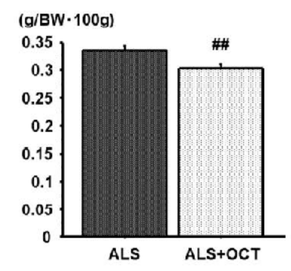
【Evaluation of RAS: study ①】



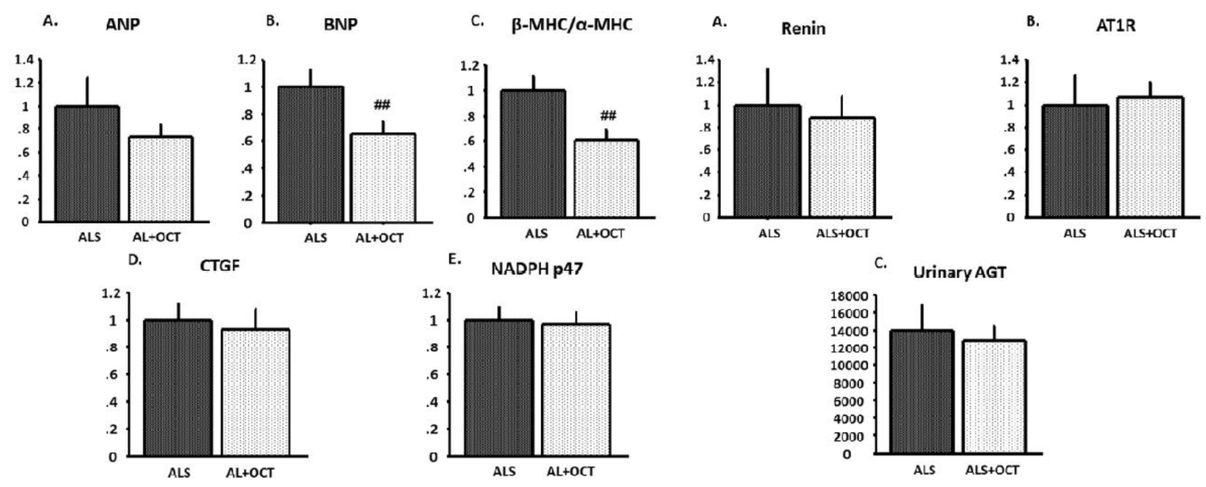
【Study ② protocol】



Heart volume: study ②



【mRNA expression of cardiac hypertrophy-related genes: study ②】【Evaluation of RAS: study ②】



- ✓ At 30 weeks of age, despite comparable blood pressure and renal function, urinary excretion of 8-hydroxydeoxyguanosine (8-OHdG) and serum NT-proBNP levels were significantly lower in the OCT group than in the DM group.
- ✓ Heart volume was significantly lower in the OCT group compared to the DM group.
- ✓ The number of 8-OHdG positive cardiomyocyte was reduced and cardiac and perivascular fibrosis was ameliorated by OCT administration.
- ✓ The mRNA expressions of ANP, BNP, NADPHp22 and CTGF in the heart were significantly decreased in the OCT groups compared to the DM group.
- ✓ Heart volume and the mRNA expressions of cardiac hypertrophy markers were lower in the AL+OCT groups compared to the AL group though urinary excretion of angiotensinogen and the mRNA expressions of renin and angiontesinogen did not differ between the two groups.

Conclusion

Oxidative stress may play a key role for development of cardiac hypertrophy and cardiac fibrosis in DM. Furthermore, it is suggested that OCT prevented the development of cardiac damage in DM independently of RAS inhibition.

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