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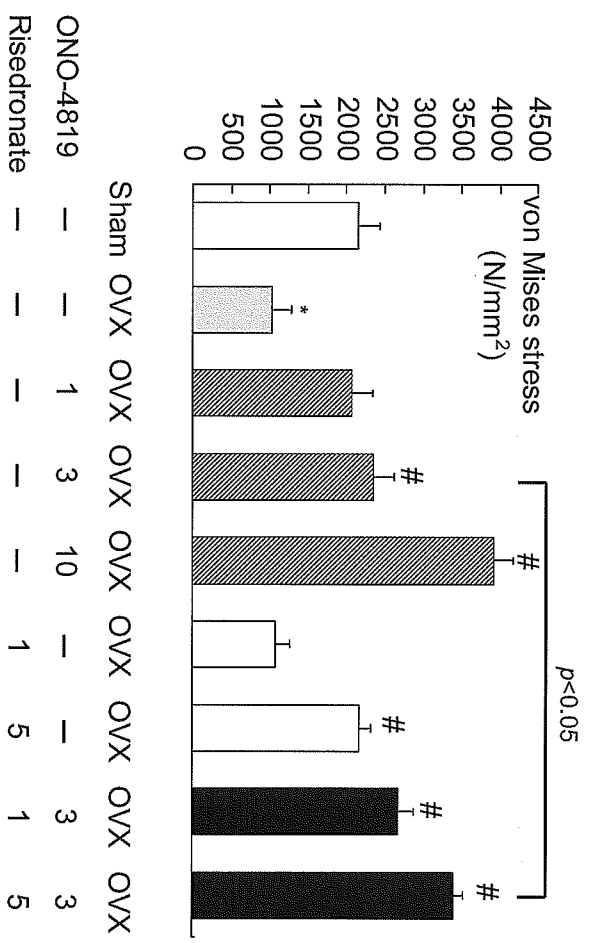


Fig.1

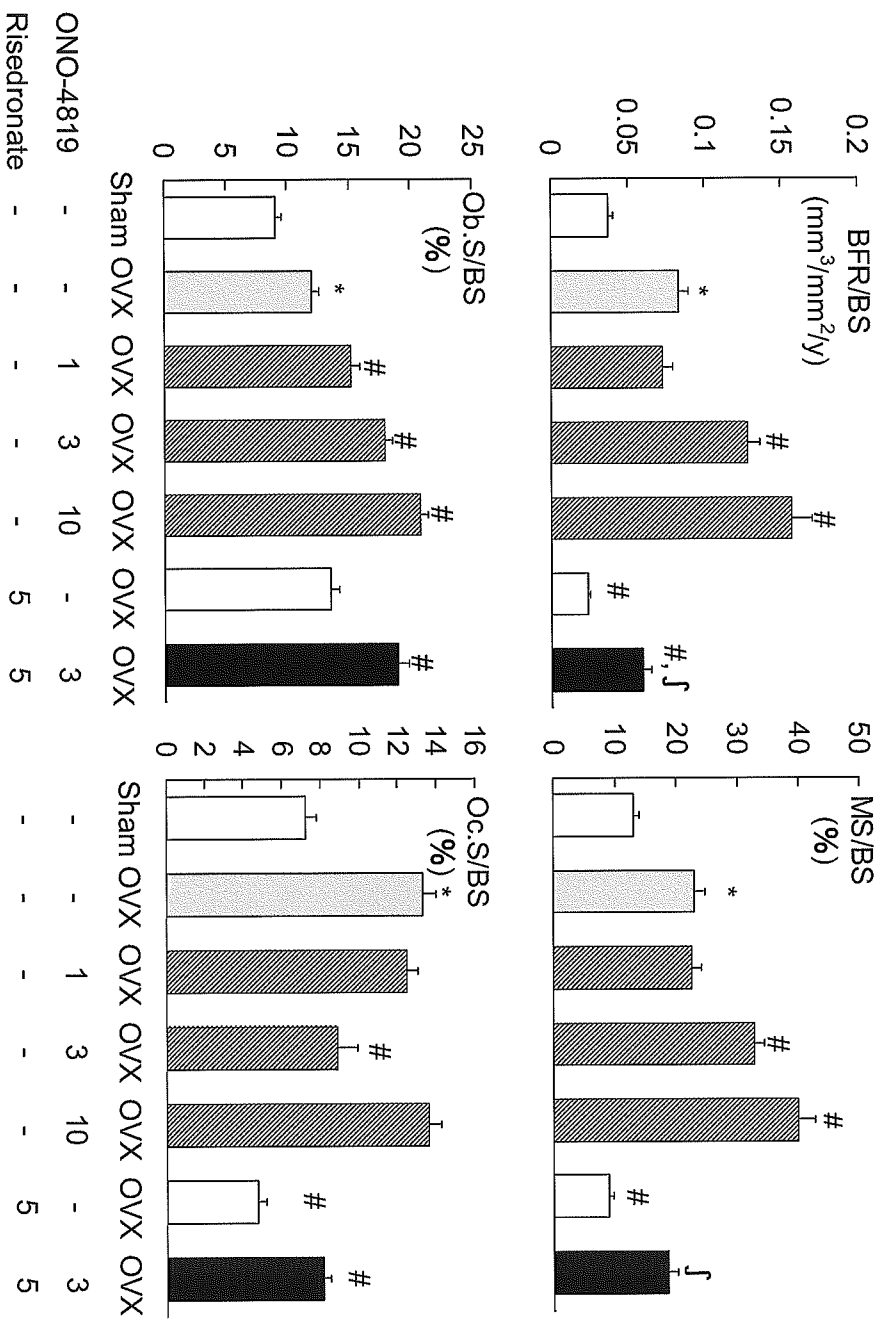


Fig.2

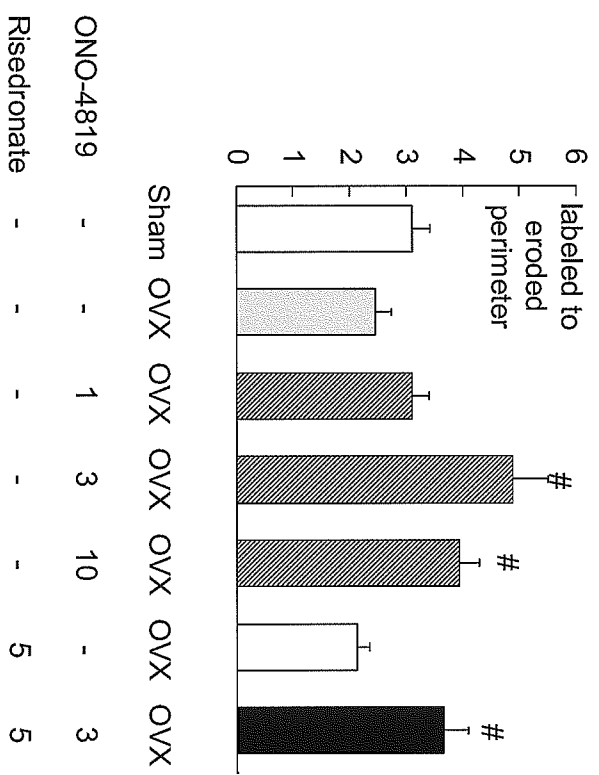


Fig.3

Table 1 Effects of ONO-4819 and risedronate on trabecular and cortical bone density in OVX rats

operation	treatment	dose µg/kg BW	trabecular BMD mg/cm ³	cortical density mg/cm ³
sham	vehicle	-	407±17	311±9
OVX	vehicle	-	220±22 [*]	255±11 [*]
OVX	ONO-4819	1	295±120	287±12
OVX	ONO-4819	3	378±178 [#]	317±7 [#]
OVX	ONO-4819	10	469±33 [#]	364±15 [#]
OVX	Risedronate	1	308±12 [#]	294±5
OVX	Risedronate	5	346±23 [#]	320±12 [#]
OVX	ONO-4819 + Risedronate	3 + 1	393±26 [#]	338±9 [#]
OVX	ONO-4819 + Risedronate	3 + 5	453±17 ^{#§}	331±7 [#]

33-week-old OVX rats were treated with the indicated drugs for 11 weeks. BMD of trabecular and cortical compartments at the tibiae was determined separately.

Cortical density is expressed as mg/cm³ hydroxyapatite equivalent. Data are shown as Mean±S.E. (n = 10 per group).

^{*}p<0.05 vs. sham group (by Wilcoxon rank sum test), [#]p<0.05 vs. OVX group (by Wilcoxon rank sum test), [§]p<0.05 vs. ONO-4819 (3µg/kg) alone (by Steel test)

Table 2. Effects of ONO-4819 and risedronate on microstructural parameters at tibiae of OVX rats

operation	treatment	dose µg/kg BW	BV/TV	Tb.N 1/mm	Tb.Th mm	SMI	ConnD. 1/mm ³
sham	vehicle	-	0.236±0.014	3.89±0.16	0.061±0.002	1.42±0.13	94.61±9.13
OVX	vehicle	-	0.109±0.010 [*]	2.03±0.18 [*]	0.053±0.001 [*]	2.16±0.08 [*]	30.65±4.05 [*]
OVX	ONO-4819	1	0.160±0.014	2.70±0.17	0.059±0.002	1.83±0.10	47.82±5.03
OVX	ONO-4819	3	0.185±0.009 [#]	3.07±0.16 [#]	0.061±0.001 [#]	1.45±0.04 [#]	59.19±5.87 [#]
OVX	ONO-4819	10	0.315±0.023 ^{#,†}	3.86±0.23 [#]	0.081±0.002 ^{#,†}	0.33±0.17 ^{#,†}	69.26±7.37 [#]
OVX	Risedronate	1	0.140±0.011	2.73±0.15 [#]	0.051±0.002	2.26±0.10 [†]	51.94±5.29 [#]
OVX	Risedronate	5	0.187±0.019 [#]	3.22±0.20 [#]	0.057±0.003	1.88±0.13	71.32±6.19 [#]
OVX	ONO-4819 + Risedronate	3 + 1	0.228±0.021 [#]	3.43±0.18 [#]	0.066±0.003 [#]	1.21±0.17 [#]	63.86±4.92 [#]
OVX	ONO-4819 + Risedronate	3 + 5	0.272±0.014 ^{#,§}	3.97±0.11 ^{#,§}	0.068±0.002 ^{#,§}	1.02±0.12 ^{#,§}	89.36±3.77 ^{#,§}

33-week-old OVX rats were treated with the indicated drugs for 11 weeks. Microstructural parameters were determined by using micro CT, as described in the Methods. Data are shown as Mean±S.E. (n = 10 per group).

^{*}p<0.05 vs. sham group (by Wilcoxon rank sum test), [#]p<0.05 vs. OVX group (by Wilcoxon rank sum test), [†]vs. sham group (by Wilcoxon rank sum test), [§]p<0.05 vs. ONO-4819 (3µg/kg) alone (by Steel test)

BV/TV: bone volume/tissue volume, Tb.N: trabecular number, Tb.Th: trabecular thickness, Tb.Sp: trabecular separation, SMI: structure model index, ConnD.: connectivity density

Table 3 The additive effects of ONO-4819 and risedronate on BMD, bone geometry, microstructural parameters and biomechanical properties

	ONO-4819 ^a	risedronate ⁱ	ONO-4819 + risedronate Interaction ^a	additive ^b	
BMD and geometry	trabecular BMD	0.001	0.001	0.208	YES
	cortical density	0.001	0.001	0.013	NO
	cortical thickness	0.01	NS	0.439	YES
microstructural parameters	BV/TV	0.001	0.001	0.821	YES
	Tb.N	0.01	0.01	0.531	YES
	Tb.Th	0.05	0.01	0.513	YES
	Tb.Sp	0.01	0.001	0.176	YES
	SMI	0.001	0.01	0.474	YES
	ConnD	0.001	0.001	0.308	YES
	DA	NS	NS	0.882	YES
finite element analysis ⁱ	von Mises stress	0.001	0.001	0.658	YES

^a p value obtained from a two-way ANOVA analysis model on rank transformed data

^b The effects of ONO-4819 and risedronate were considered to be additive and independent of each other if the interaction effect was not statistically significant.

BV/TV: bone volume/tissue volume, Tb.N: trabecular number, Tb.Th: trabecular thickness, Tb.Sp: trabecular separation, SMI: structure model index, ConnD: connectivity density, DA: degree of anisotropy