

The Effects of Coenzyme Q10 in Sirolimus-Induced Pancreatic Islet Injury

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Background

This study was performed to investigate the effect of addition of coenzyme Q₁₀ (CoQ₁₀) to metformin (MET) on sirolimus (SRL)-induced diabetes mellitus (DM).

Patients and Methods

Animal model of SRL-induced DM was induced with daily treatment of SRL (0.3 mg/kg, s.c.) for 28 days, and CoQ₁₀ (20mg/kg, p.o.) or metformin (250mg/kg, p.o.) was treatment alone or combination for 14 days. The effect of MET and CoQ₁₀ on SRL-induced DM was evaluated by assessing by measuring of pancreatic islet function (blood glucose level and insulin secretion) and oxidative stress and apoptosis.

Results

Table 1. Basic parameters in basic groups

	VH (n=9)	SRL (n=9)	SRL+CoQ ₁₀ (n=9)	SRL+MET (n=9)	SRL+CoQ ₁₀ +MET (n=9)
Δ BW (g)	85 ± 5	19 ± 4*	25 ± 3	41 ± 2†	62 ± 3†§
UV (mL)	14 ± 2	20 ± 3*	17 ± 2	12 ± 3†	13 ± 2†
Water intake (mL)	18 ± 4	30 ± 5*	25 ± 6	22 ± 5†	19 ± 5†
Scr (mg/dL)	0.35 ± 0.04	0.30 ± 0.03	0.34 ± 0.15	0.31 ± 0.06	0.31 ± 0.05
HbA1C (%)	3.93 ± 0.12	3.94 ± 0.15	4.02 ± 0.19	3.94 ± 0.20	3.93 ± 0.13
SRL con. (ng/mL)		7.26 ± 2.99	6.10 ± 3.11	6.06 ± 2.80	5.88 ± 2.31

Abbreviation: n, No. of animals; BW, body weight; UV, urine volume; Scr, serum creatinine; SRC con., sirolimus concentration; HbA1C, hemoglobin A1C; VH, vehicle; SRL, sirolimus; CoQ₁₀, coenzyme Q10; MET, metformin. Values are means ± standard error.

*P < 0.05 vs. VH, †P < 0.05 vs. SRL, §P < 0.05 vs. SRL+MET

Table 2. Effects of combination treatment of CoQ₁₀ MET on control of SRL-induced hyperglycemia using IPGTT

Group	0 min	30 min	60 min	90 min	120 min	AUCg
VH	90 ± 3	210 ± 10	145 ± 5	137 ± 5	108 ± 3	295 ± 9
SRL	83 ± 4	316 ± 20*	250 ± 9*	178 ± 7*	132 ± 2	424 ± 17*
SRL+ CoQ ₁₀	81 ± 3	312 ± 18*	225 ± 7*	144 ± 4	106 ± 4	386 ± 12
SRL+MET	80 ± 4	275 ± 16*	176 ± 6†	128 ± 3†	106 ± 3	335 ± 14†
SRL+ CoQ ₁₀ +MET	83 ± 3	242 ± 15†§	144 ± 5†§	108 ± 2†	93 ± 2†	291 ± 15†§

Abbreviation: VH, vehicle; SRL, sirolimus; CoQ₁₀, coenzyme Q10; MET, metformin. Values are means ± standard error.

*P < 0.05 vs. VH, †P < 0.05 vs. SRL, §P < 0.05 vs. SRL+MET

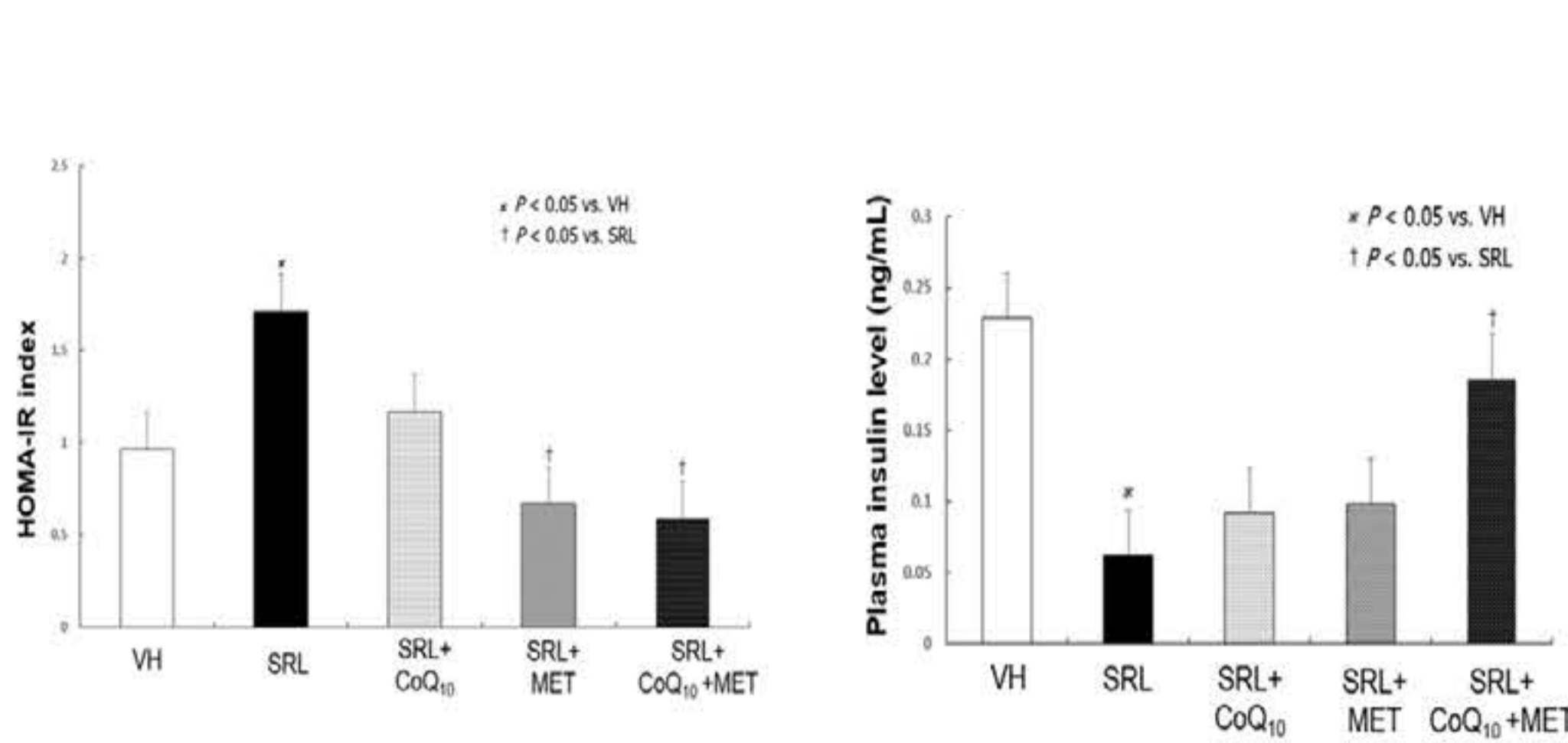


Figure 1. Four weeks of SRL treatment increased the homeostatic model assessment of insulin resistance (HOMA-IR) index, and decreased insulin level. MET or CoQ₁₀ + MET reverted these changes, as it decreased HOMA-IR, and increased insulin level compared with SRL group.

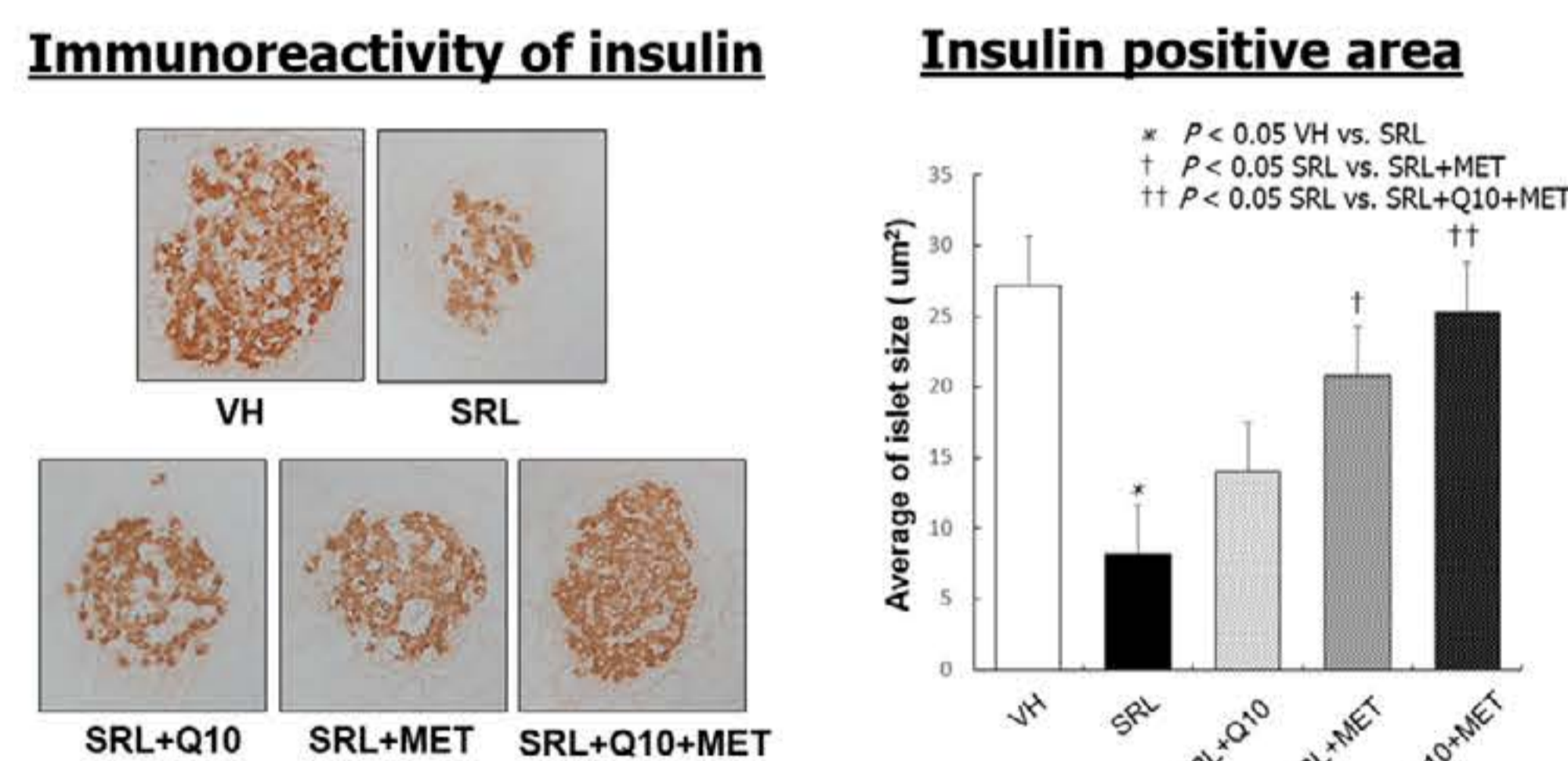


Figure 2. The SRL group showed a smaller islet with lower intensity of insulin staining within islet. Although this effect was not reverted by CoQ₁₀ alone therapy, treatment with MET and CoQ₁₀ + MET showed a significant improvement in intensities of insulin staining within islet.

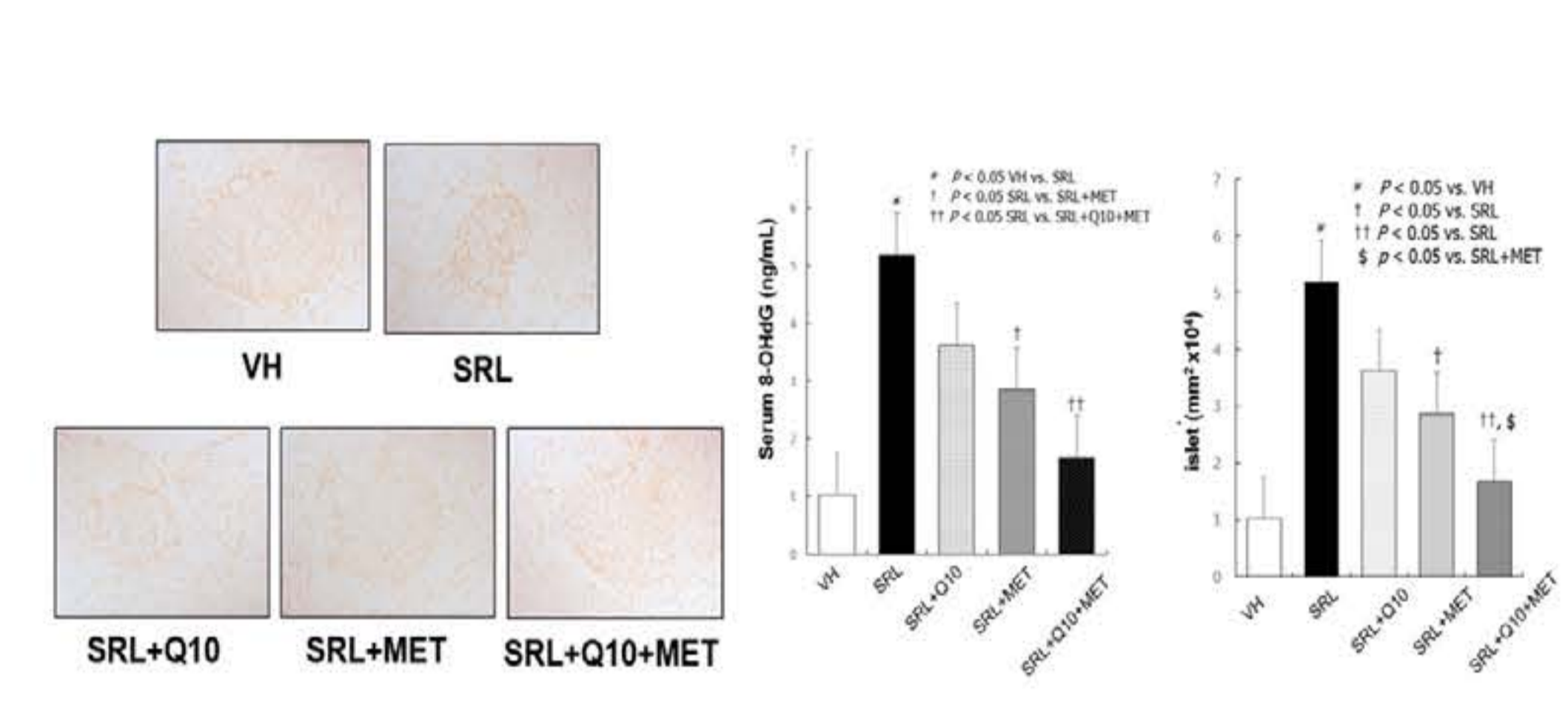


Figure 3. A higher level of 8-OHdG in the serum was also detected in the SRL group; MET or CoQ₁₀ + MET treatment significantly decreased these changes. Concomitant administration of CoQ₁₀ and MET reduced significantly (P < 0.05) 8-OHdG levels in serum and islets as compared to MET alone treatment.

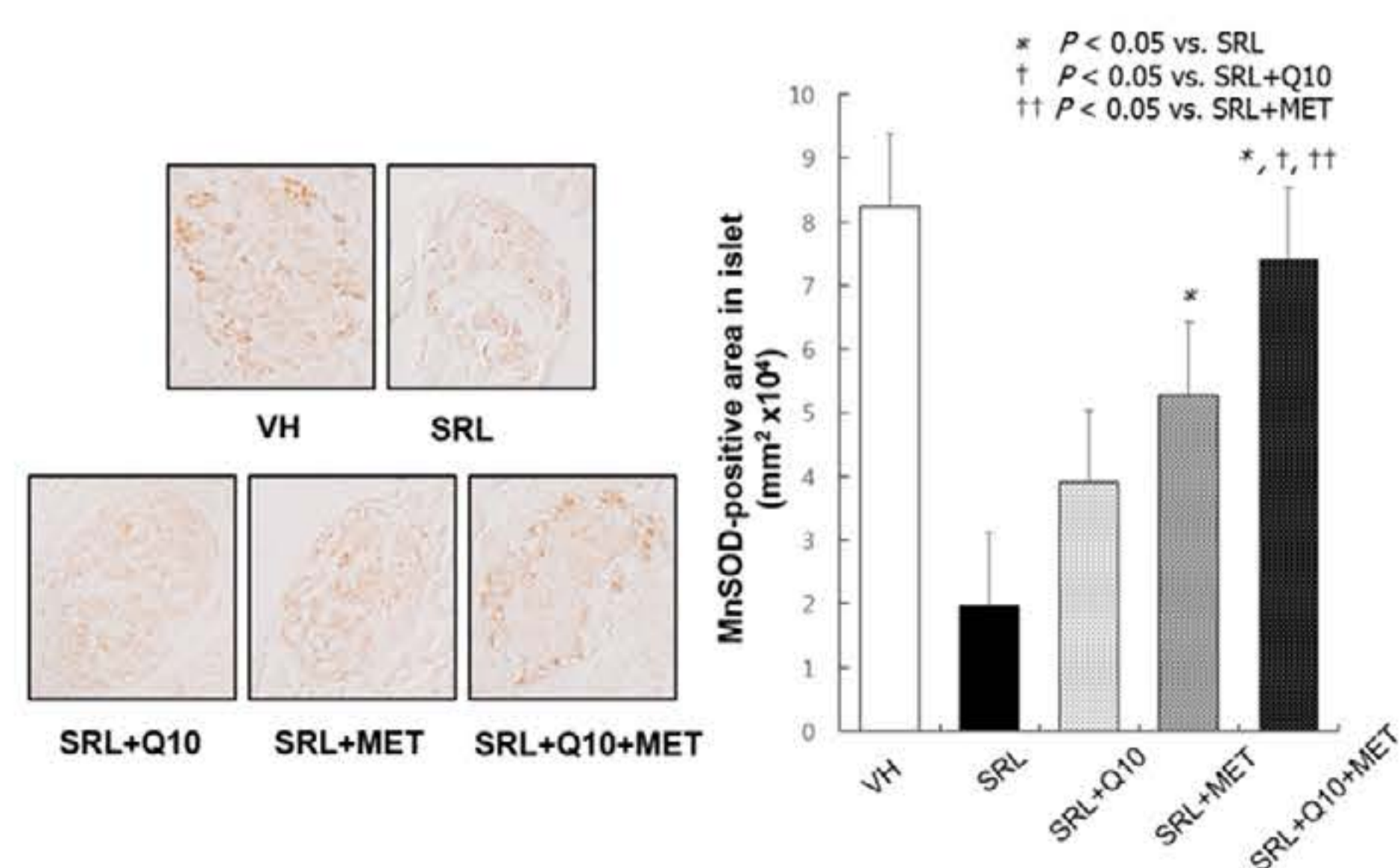


Figure 4. The rats in SRL group showed a significant (P < 0.001) decrease in the levels of antiperoxidative enzymes (MnSOD) in renal tissue as compared to normal control group. However, treatment with MET or CoQ₁₀ + MET increased in MnSOD activities in renal tissue.

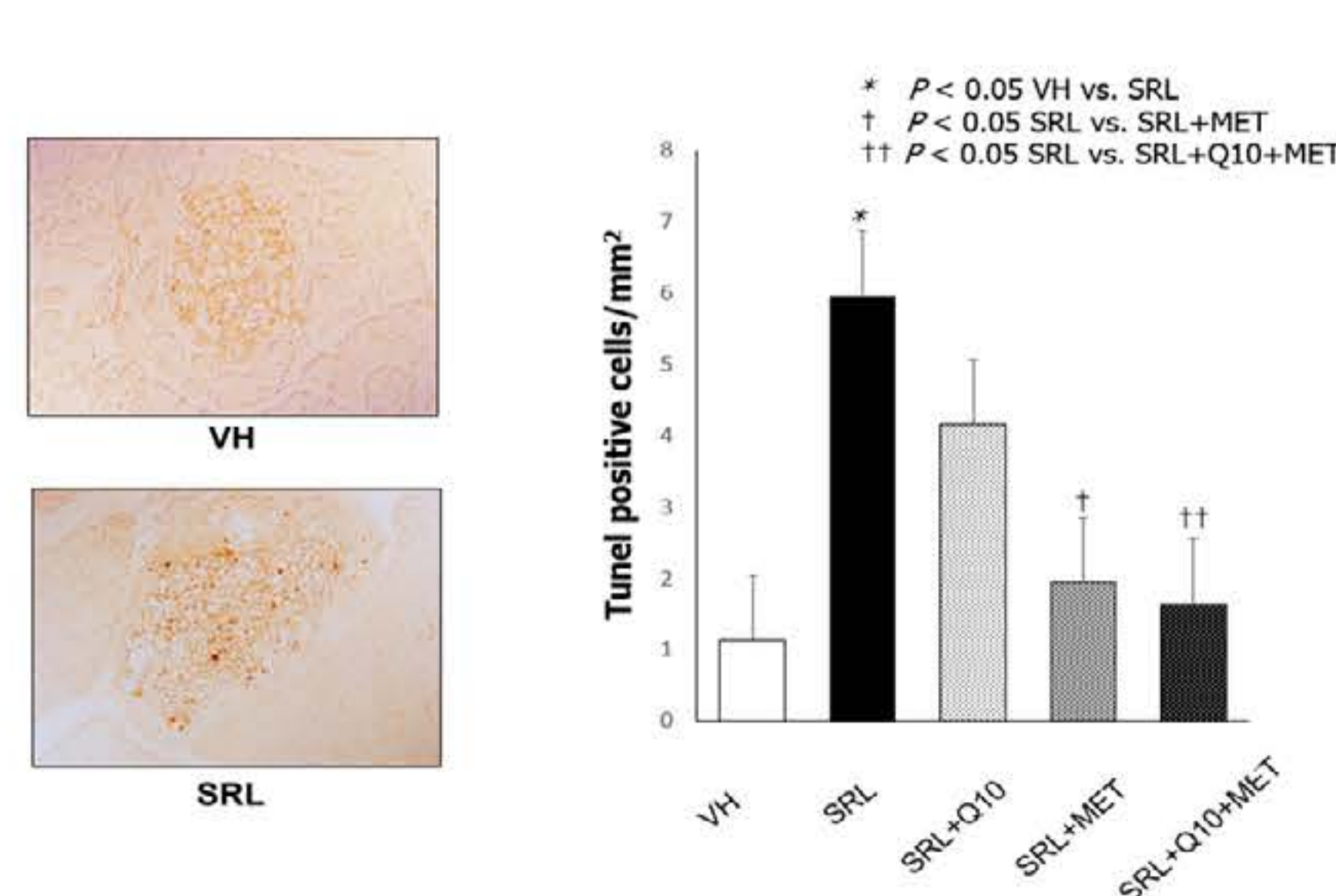


Figure 5. The number of TUNEL-positive cells in tissue sections was significantly higher in the SRL-group compared with the VH group, and CoQ₁₀ + MET and MET alone treatment decreased significantly (P < 0.05) the number of TUNEL-positive cells in tissue sections.

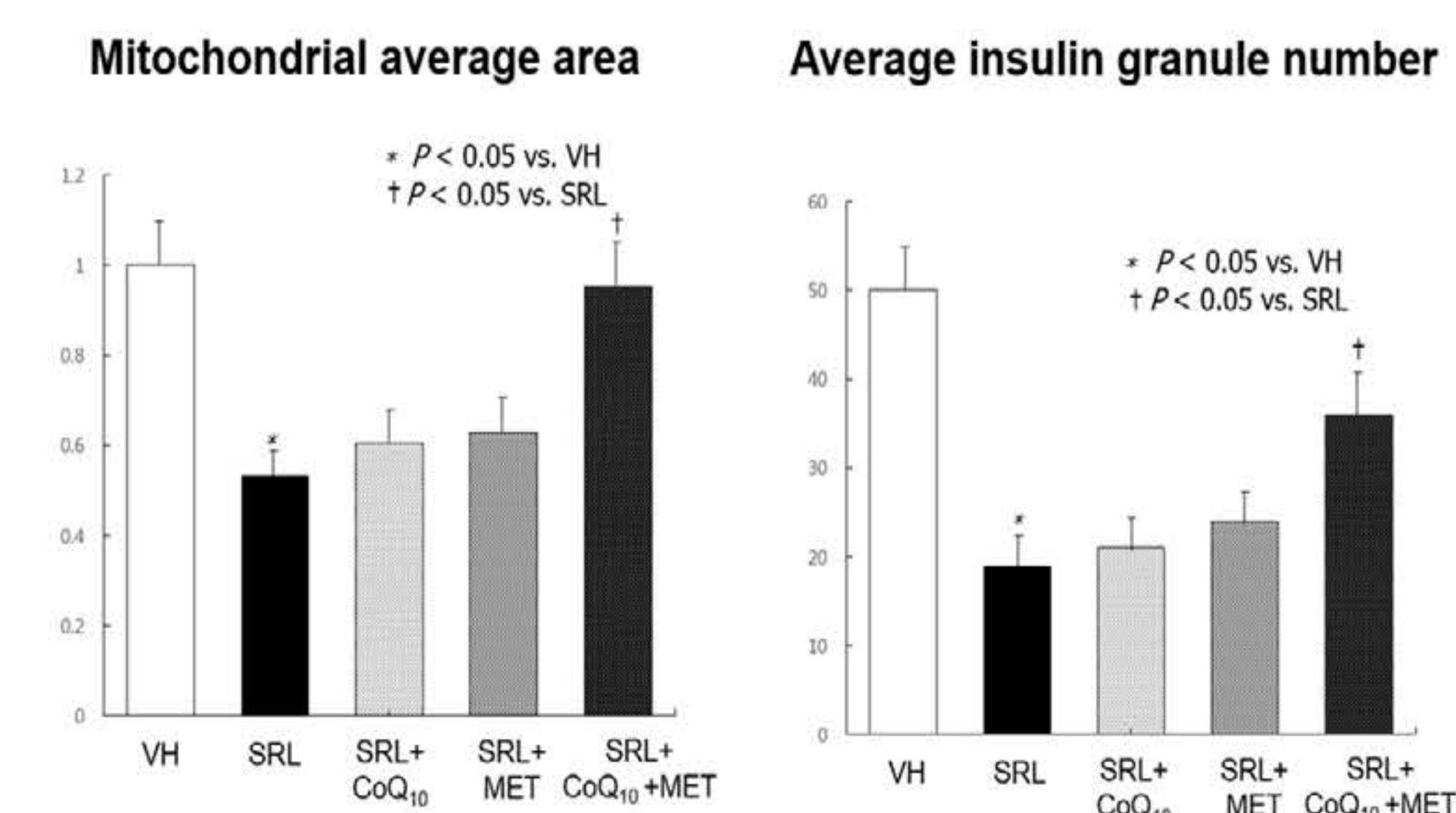


Figure 6. Although CoQ₁₀ or MET alone therapy could not protect the decrease, concomitant administration of CoQ₁₀ and MET restored the average mitochondrial area and insulin granule number.

Summary and Conclusion

Combined use of MET and CoQ₁₀ had more protective effect against SRL-induced pancreatic injury than MET alone therapy.