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ORAL ADMINISTRATION OF DOXYCYCLINE PREVENTS VULNERABLE PLAQUES FROM RUPTURE INDEPENDENT OF SERUM LIPID LEVELS (AN ANIMAL EXPERIMENT WITH RABBITS)

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Objectives Chronic inflammatory responses have been implicated in the process of atherosclerosis. Doxycycline, as a broad spectrum antibiotic, has also proven effective in inhibiting MMP. The aim of this study was to evaluate the effect of doxycycline treatment on

stabilising the vulnerable plaque in the New Zealand white rabbits.

Methods Thirty New Zealand white rabbits were then randomly divided into group A (n=10), group B (n=10), group C (n=10). All underwent balloon-induced abdominal aortic endothelial injury and were fed a diet of 1% cholesterol for 8 weeks. The rabbits in Group A were given doxycycline (10 mg/kg/d). The rabbits in Group B were given simvastatin (5 mg/kg/d). The rabbits in Group C were the control group. All three groups were given high cholesterol food. 12 weeks later, pharmacological triggering was performed with the injection of Chinese Russell's viper venom and histamine in both groups. The concentration of doxycycline in rabbit's plasma was determined by HPLC. Serum lipids and inflammatory markers were measured and high frequency ultrasonography and intravascular ultrasound (IVUS) imaging were performed to measure the intimal media thickness (IMT), the external elastic membrane area (EEMA), the plaque area (pA) and the plaque burden (PB) of the abdominal aorta. Plaque contents were evaluated by immunohistochemistry and the vulnerability index (VI) was calculated. The mRNA expressions of inflammatory markers in the plaques were assessed by RT-PCR.

Results The results showed that doxycycline resulted in a significant inhibition of IMT ($p < 0.05$) (A: 0.84 ± 0.16 mm; B: 0.79 ± 0.14 mm; C: 1.33 ± 0.26 mm) and significantly increased the thickness of the plaque caps (A: 257 ± 62 μ m; B: 283 ± 72 μ m; C: 123 ± 52 μ m) and decreased VI, IMT, EEMA, PA, PB% in doxycycline treatment group (all $p < 0.05$), there was significant difference in vulnerability index in doxycycline treatment group ($p < 0.05$) (A: 0.72 ± 0.08 ; B: 0.52 ± 0.10 ; C: 3.71 ± 0.21). There was no significant difference in serum lipid levels in doxycycline treatment group, but the serum levels and the mRNA and protein expressions of inflammatory markers were significantly reduced in doxycycline treatment group ($p < 0.05$) (Serum Inflammatory Markers in three Groups: hs-CRP A: 45.2 ± 11.5 ng/ml, B: 40.7 ± 8.9 ng/ml, C: 127.2 ± 44.9 ng/ml; MCP-1 A: 30.4 ± 6.2 pg/ml, B: 26.8 ± 4.6 pg/ml, C: 86.3 ± 10.4 pg/ml; IL-8: A: 6.6 ± 4.2 pg/ml, B: 5.2 ± 2.7 pg/ml, C: 20.1 ± 14.7 pg/ml; IL-18: A: 55.9 ± 12.5 pg/ml, B: 34.8 ± 12.7 pg/ml, C: 92.7 ± 40.8 pg/ml; MMP-1: A: 9.3 ± 2.7 ng/ml, B: 11.7 ± 4.2 ng/ml, C: 59.4 ± 8.99 ng/ml; P-selectin: A: 10.2 ± 1.6 ng/ml, B: 7.4 ± 1.3 ng/ml, C: 32.1 ± 4.9 ng/ml. mRNA Expressions of Inflammatory Markers in three Groups: MCP-1, A: $40.41 \pm 9.78\%$, B: $30.72 \pm 8.73\%$, C: $63.87 \pm 6.23\%$; MMP-1: A: $10.87 \pm 3.70\%$, B: $12.87 \pm 3.62\%$, C: $49.43 \pm 11.20\%$; MMP-3: A: $4.30 \pm 5.22\%$, B: $5.43 \pm 3.85\%$, C: $33.51 \pm 9.82\%$; MMP-12: A: $6.93 \pm 5.05\%$, B: $7.43 \pm 2.51\%$, C: $36.02 \pm 8.72\%$, P-selectin: A: $20.94 \pm 6.09\%$, B: $10.87 \pm 6.03\%$, C: $48.78 \pm 6.23\%$)

Conclusions Doxycycline effectively inhibits plaque inflammation and prevents vulnerable plaques from rupture. These therapeutic effects are independent of serum lipid levels and demonstrate the concept that inhibition of plaque inflammation alone without lipid lowering can stabilise vulnerable plaques.