Liposomal prednisolone promotes macrophage necroptosis in experimental atherosclerosis: does this explain atherogenesis in Cushing’s disease?

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**Rationale:** Liposomal nanoparticles loaded with prednisolone (LN-PLP) have previously been reported to accumulate in macrophages of rabbits’ atherosclerotic lesions, and rapidly reduce arterial wall inflammation. In patients with atherosclerotic disease, accumulation of LN-PLP in macrophages of atherosclerotic plaques has been demonstrated, but arterial wall inflammation reduction was not observed.

**Objective:** To evaluate the effect of LN-PLP’s effect on inflammatory macrophages in a mouse model of atherosclerosis.

**Methods and Results:** In low-density lipoprotein receptor knockout (LDLr−/−) mice on high-fat diet, we show that LN-PLP accumulates in plaque macrophages and biweekly injections at 10mg/kg induces (i) enhanced monocyte recruitment to the plaque, leading to (ii) increased macrophage content, more advanced plaque stages, and larger necrotic core sizes after 8 weeks of treatment. *In vitro*, we observed that both murine and human macrophages polarize into a lipophilic phenotype following LN-PLP exposure, illustrated by increased lipid accumulation, endoplasmatic reticulum (ER) stress and necroptosis.

**Conclusion:** These findings indicate that local exposure to the anti-inflammatory compound prednisolone, can elicit a pro-atherogenic, lipotoxic effect in plaque macrophages. This might explain atherogenesis in patients with Cushing’s disease.

**Efficacy:** monocyte recruitment

**Efficacy:** gene expression

**Efficacy:** plaque size

**in vitro:** lipotoxicity and necroptosis

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Wissen schafft Gesundheit