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Effects Of 4-weeks’ Treatment With Intraperitoneal Colchicine On Metabolic And Inflammatory Outcomes In Mice Fed A High-fat Diet

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Health-deteriorating effects of obesity include chronic inflammation and insulin resistance (IR). A recent pilot human trial reported reduced IR in colchicine-treated vs. placebo-treated adults with obesity. Thus, we examined anti-inflammatory and metabolic effects of two commonly employed dosing regimens of colchicine, 0.2 mg/kg and 0.02 mg/kg, in a high-fat diet (HFD; 45%) mouse obesity model. We placed male C57BL/6J mice on HFD from ages 8 through 16 weeks. At age 12 weeks, mice were randomized to: high-dose colchicine (CHD 0.2 mg/kg, n=28), low dose colchicine (CLD, 0.02 mg/kg, n=26) or vehicle (V, n=26), injected intraperitoneally (IP) for 4 weeks. Serum CRP was measured by ELISA. Dual-energy X-ray absorptiometry (DXA) scans and fasting IP glucose tolerance (GTT) and insulin-tolerance (ITT) tests were performed at baseline and following treatment. Hepatic tissue was processed for immunoblotting to determine expression of NLRP3 and caspase-1. Changes in pre- vs. post-treatment serum CRP were significantly different in the CHD group (Mean±SD: -0.57±3.1µg/mL) vs. V (+3.64±2.9µg/mL; p<0.001) and CLD (+0.72±2.3µg/mL) compared to V (p=0.03). Changes in CRP for CHD compared to CLD did not differ significantly (p=0.47). DXA-measured body composition changes pre-vs. post-treatment for fat mass were significantly reduced for CHD (-0.26±2.0g) vs. V (+1.24±2.1g; p=0.04) and CHD vs. CLD (+1.52±2.2g; p=0.01). Lean body mass changes were not significant between treatments (p=0.69). GTT glucose concentrations were not significantly different between treatments across timepoints (Group x time interaction: p=0.24) and GTT areas under curves (AUC) were not significantly different between treatments (p=0.96). Analysis of ITT glucose measures revealed a significant group x time interaction (p=0.03) and group effect for CHD vs. V (p=0.009) as well as significant differences in ITT AUCs (p=0.03) such that insulin tolerance was significantly worse for CHD: CHD AUC 19803±2662, CLD 18487±3703, V 17436±3138mg/dLx120min. Hepatic NLRP3 fold-change protein expression of treatment groups compared to V was not significant for CHD (p=0.75) or CLD (p=0.21). However, hepatic caspase-1 protein expression fold-change was significantly lower in the CHD (p=0.008), but not the CLD group (p=0.19). We conclude that 4-weeks of IP colchicine at 0.2mg/kg (CHD) significantly suppressed serum CRP and hepatic caspase-1 protein expression compared to V, indicating CHD reduced inflammation, whereas 0.02mg/kg colchicine (CLD) did not. However, our data suggest that 4 weeks of the CHD dose may potentially worsen whole-body insulin resistance, even though it induced a reduction in fat mass, suggesting a possible toxicity from chronic high-dose colchicine treatment.

Further studies are warranted to elucidate metabolic effects of colchicine administration in murine diet-induced obesity models.

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