Research in Genes and Proteins

Extended Abstract
Vol. 1, Iss. 4
2019

Effects of Vitamin D Combined with Aspirin or Atorvastatin on Plasma Lipid Profiles and Lipid Peroxidation in Triton-XInduced Hyperlipidemia in Rats

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ABSTRACT

Vitamin D deficiency as an independent cardiovascular risk factor has since been related to increased risks of cardiovascular events. this study assessed the modulatory effects of posttreatment of vitamin D alone and with aspirin or atorvastatin on triton-X-induced hyperlipidemia in rats. Forty-nine (49) Wistar rats were divided into seven experimental groups of seven per group. Group A, control negative group, received no treatment. Group B-G received triton (400 mg/kg) to induce hyperlipidemia. Groups C, D and E were post-treated with vitamin D only (200 IU/kg), aspirin only (1 mg/kg), atorvastatin only (10 mg/kg) respectively. Groups F and G were post-treated with vitamin D together with either aspirin or atorvastatin. Results obtained showed increased MDA(an indicator of lipid peroxidation) levels in B animals [rats that received triton (400 mg/kg) only and not treated with any drug] by 77.4% and an elevation of rarity lipoprotein (LDL) by 65.8% in comparison with control negative group($p< 0.05$). Similarly, high density lipoprotein (HDL) deceased during this group of rats that received triton only ($p> 0.05$). vitamin D (200IU/kg), aspirin (1mg/ kg) and atorvastatin (10mg/kg) didn't significantly ($p> 0.05$) alter total cholesterol TC, TG, HDL, LDL and malondialdehyde (MDA) levels respectively when administered alone. However, vitamin D plus aspirin or atorvastatin treated animals reduced triton-induced lipid profile and MDA, although not statistically significant ($p> 0.05$). last, this present study suggested vitamin D possesses lipids and lipid peroxidation lowering activity. Thus, vitamin D supplementation could offer chemoprevention during this condition. Hyperlipidemic rat model was produced by high-fat and high-cholesterol diet for six weeks. Rats with normal diet were served as shame group. In hyperlipidemic group, normal saline, atorvastatin (10 mg/kg body weight/day), colchicines (0.5 mg/kg body weight/day), or atorvastatin combined with colchicines (same dosages) were prescribed for two weeks. Serum levels of lipid profile, C-reactive protein (CRP), liver enzyme, lipoprotein associated phospholipase A2 (Lp-PLA2) and gas (NO) production were serially assessed. Before the start of the study, all laboratory variables were comparable among each group. After 6 weeks of hyperlipidemic model production, serum levels of cholesterols, CRP and Lp-PLA2 were significantly increased in comparison to sham group, whereas NO production was reduced. With 2 weeks of colchicine therapy, serum levels of CRP and Lp-PLA2 were decreased and NO production was enhanced within the colchicine group during a lipid-lowering independent manner. Added colchicine into atorvastatin therapy further improved NO production and decreased CRP and Lp-PLA2 levels, indicating a

This work is partly presented at 10th International Conference on Genomics and Molecular Biology, May 21-23, 2018 Barcelona, Spain

possible synergism of colchicine and atorvastatin.

Colchicine combined with atorvastatin may have stronger protective effects on improving endothelial function and ameliorating inflammation in rats with hyperlipidemia. Hyperlipidemia may be a major explanation for multiple diseases like atherosclerotic cardiovascular diseases (CVD). The mechanisms of hyperlipidemia implicated within the initiation and progression of CVD predominantly involve sustained endothelial dysfunction and vascular inflammation. Previously, many animal studies and clinical trials even have consistently demonstrated that with statins therapy, a potent agent in regulating lipid metabolism, not only lipid profile disorder has been corrected but also systemic inflammation is ameliorated as indicated by the decrease of inflammatory cytokines like C-reactiveprotein (CRP).

Lipoprotein associated phospholipase A2 (Lp-PLA2) may be a key enzyme liable for degrading platelet-activating factor (PAF) and oxidated-LDL (ox-LDL). Initially, some basic studies showed that Lp-PLA2 was beneficial for deterring atherosclerosis progression by means of degrading PAF, a potent pro-inflammatory cytokine. Nevertheless, thereafter, an outsized number of clinical and experimental studies have consistently revealed that increased Lp-PLA2 level was related to increased risk of cardiovascular events, which was considered to be related to the increased production of lyso-phosphotidylcholine (Lyso-PC) and oxidized non-esterified fatty acids (oxNEFAs), two potent pro-inflammatory and pro-atherosclerotic intermediates derived from ox-LDL degradation by Lp-PLA2. Notably, some studies showed that statins may need effects on reducing Lp-PLA2 level, nonetheless, other studies showed no favorable effects of statins on Lp-PLA2 reduction. Therefore, whether statins can reduce Lp-PLA2 remains inconclusive.

Colchicine is an old medicine and has been used for gout and other inflammatory diseases thanks to its potent effect on improving inflammatory reactions. Recently, a study conducted by Nidorf and colleagues showed that colchicine combined with statins was beneficial for cardiovascular events' prevention. The underlying mechanisms are faraway from clear, however. Previously, one study revealed that colchicine could inhibit adhesion of neutrophilic granulocytes to epidermal sections induced by PAF. Since most of circulating Lp-PLA2 is produced by macrophages within vascular wall, therefore, we hypothesized that colchicine might reduce Lp-PLA2 production through inhibiting leukocytes adhesion and infiltration.

Taken together, in light of the crucial roles Lp-PLA2 plays on the initiation and progression of vascular inflammation and atherosclerosis in subjects with hyperlipidemia and therefore the potent effect of colchicine on regulating inflammation, we hypothesized that colchicine could be effective in ameliorating vascular inflammation and improving endothelial function by means of declining Lp-PLA2 level, and if corroborated, we believed that within the future adds colchicines into statins therapy may have additional benefits on CVD prevention and therapy.

Keywords: Vitamin D; Triton; hyperlipidemia; lipid peroxidation