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Colchicine's Effects on Lipoprotein Particle Concentrations in Adults with Metabolic Syndrome: A Secondary Analysis of a Randomized Controlled Trial

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Abstract

Background—Colchicine has received renewed interest for its potential beneficial effects in secondary prevention of cardiovascular disease. This has presumed to be primarily due to its anti-inflammatory effects; however, limited data exist regarding colchicine's impact on other cardiovascular risk factors.

Objective—To examine if colchicine's anti-inflammatory actions would lead to reduced circulating concentrations of oxidized low-density lipoprotein (oxLDL) in metabolically unhealthy individuals. We also examined if colchicine would improve concentrations of other atherogenic lipoprotein subfractions.

Methods—This is a secondary analysis of a double-blind, randomized, placebo-controlled pilot study in which 40 adults with metabolic syndrome were randomized to colchicine 0.6mg or placebo twice daily for three months. Blood samples were collected in the fasted state. OxLDL was measured using enzyme-linked immunosorbent assay. Nuclear magnetic resonance spectroscopy was used to measure other lipoprotein particle subfraction concentrations.

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Authors' contributions

The study was designed by JAY and APD. Data were collected by APD, SRW, AW, JAL, AVS, SMB, AR, and JAY. Statistical analyses were conducted by APD and JAY, who wrote the first draft of the manuscript. All authors provided critical review of the manuscript and had final approval of the submitted and published versions.

Trial Registration: www.clinicaltrials.gov (, registered May 31, 2014).

Results—As compared with placebo, colchicine reduced markers of inflammation, including C-reactive protein, erythrocyte sedimentation rate, and GlycA (p's<0.01). Concentrations of oxLDL (p=0.019) and small LDL (p=0.022) appeared significantly increased in the colchicine arm. Colchicine had no significant effect on other lipoprotein subfractions or lipoprotein particle sizes (all p>0.05).

Conclusion—Although colchicine may have benefit in secondary prevention of cardiovascular disease in at-risk individuals, we found no evidence that these effects are due to improvements in circulating atherogenic lipoprotein particle concentrations. Further studies are needed to confirm whether colchicine increases circulating oxLDL and small LDL levels in adults with metabolic syndrome. If true, additional research is warranted to elucidate the mechanisms underlying this association.

Keywords

Colchicine; cardiovascular disease; atherosclerosis; oxLDL; lipoprotein particles; obesity; inflammation

Introduction

Colchicine, a well-known microtubule inhibitor, is an ancient drug traditionally used to treat rheumatologic conditions such as gout and Familial Mediterranean Fever (FMF). By blocking microtubule formation and propagation, colchicine suppresses inflammation by inhibiting leukocyte locomotion and diapedesis, inflammasome formation, cytokine production and reactive oxygen species (ROS) formation [1, 2].

Recently, colchicine has enjoyed renewed interest for its potential beneficial effects in secondary prevention of cardiovascular disease (CVD) [3, 4]. In patients with diabetes undergoing percutaneous coronary intervention with bare metal stent placement, subjects randomized to colchicine 0.5mg twice daily had a significantly lower in-stent restenosis rate and decreased neointimal hyperplasia as compared to those on placebo [5]. In the LoDoCo study, subjects with stable CVD randomized to colchicine had a reduced composite endpoint of acute coronary syndrome (ACS), out-of-hospital cardiac arrest, or noncardioembolic ischemic stroke [6]. Additionally, among patients with recent ACS, colchicine use was associated with decreased unstable plaque burden [7].

Its main cardioprotective mechanism is thought to be due suppression of vascular inflammation, thereby stabilizing the atherosclerotic plaque. Colchicine has been shown to decrease C-reactive protein (CRP) and inflammatory cytokine serum concentrations in individuals with coronary artery disease and stroke [8–10] and to suppress circulating neutrophil and monocyte populations in subjects with metabolic syndrome [11].

However, as microtubules are ubiquitous and are involved in many pathways, it is possible that colchicine also exerts its cardioprotective benefits via other mechanisms. In studies of rats, colchicine inhibited hepatic secretion of lipoproteins, particularly very low-density lipoprotein-cholesterol (VLDL-C) [12, 13]. Additionally, colchicine has been shown to block micelle and triglyceride transepithelial transport in the small intestine [14, 15]. In

human clinical studies, circulating low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), or triglyceride (TG) concentrations have not been found to be significantly affected by colchicine [7, 11]. However, to our knowledge, colchicine's effects on specific atherogenic lipoprotein subpopulations are not known and thus might represent important mechanisms by which colchicine exerts its cardioprotective effects. Herein, we describe the results of a secondary analysis of a randomized controlled trial examining colchicine's metabolic effects in adults with obesity and metabolic syndrome (MetS). Because colchicine is known to decrease ROS formation, we hypothesized that oxidized LDL (oxLDL) concentrations would be significantly decreased in subjects randomized to colchicine as compared to placebo.

Materials and Methods

Participants

The detailed methods of the randomized clinical trial have been published previously [11]. Briefly, a convenience sample of adults (age ≥ 18 years) with obesity (BMI ≥ 30 kg/m^2) were studied at the National Institutes of Health Clinical Research Center (NIH CRC) in Bethesda, MD between 2014 and 2018. Participants were required to have insulin resistance (as defined by a Homeostatic Model of Insulin Resistance ≥ 2.6), chronic inflammation (as evidenced by high-sensitivity C-reactive protein [hsCRP] ≥ 2.0 mg/L), and MetS [16] to be eligible for participation. Individuals with significant chronic medical conditions including diabetes mellitus or taking medications affecting glycemia (e.g. metformin, insulin), body weight, inflammation (e.g. steroids, NSAIDs), or lipids/cholesterol (e.g. statins, fibrates) were excluded from the study.

Study Design

We conducted a single-center double-blind, randomized, placebo-controlled parallel groups phase II trial. Participants underwent a screening visit followed by a 3-month randomized double-blind treatment period. Participants were randomized in a 1:1 ratio to receive colchicine (Spectrum Chemical MFG Corp, New Brunswick, NJ) or placebo capsules, twice daily. The primary outcome of the RCT was change in insulin sensitivity, as estimated by using minimal model analysis of insulin-modified frequently-sampled intravenous glucose tolerance tests [11]. An Investigational New Drug application (#120722) to use colchicine USP was approved by the United States Food and Drug Administration. Identically-appearing placebo capsules and colchicine capsules (0.6mg/capsule) were prepared by the NIH CRC Pharmaceutical Development Section or Pine Pharmaceuticals (Tonawanda, NY). No participant, investigator, or other medical or nursing staff interacting with participants was aware of study group assignments during the trial.

Ethics approval and consent to participate

The study protocol was approved by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Internal Review Board. The study was overseen by a Data and Safety Monitoring Board convened by NICHD. All participants provided written informed consent prior to study participation.

Clinical Assessment and Lipoprotein Analyses

Assessments were performed at baseline and after 3 months of study drug. Fat mass was assessed by dual-energy x-ray absorptiometry (GE Lunar iDXA, GE Healthcare, Madison WI; software GE enCore 15 with CoreScan algorithm) [17]. Peripheral blood was collected after overnight fasting in EDTA tubes and centrifuged for 20 min at 3500 rpm. Obtained plasma was immediately stored at –80°C until further analysis without being exposed to freeze-thaw cycles. Plasma levels of oxLDL (U/L) were determined by anti-ApoB-100 conformational epitope 4E6 antibody (Mercodia, Uppsala, Sweden, CAT# 10–1143-01). The intra-assay coefficient of variation (CV) was 7.4%, and the inter-assay CV was 1.6%. Each sample was run in duplicate wells and the average values were used in the analyses. Concentrations of other plasma lipoprotein subfractions (e.g. three VLDL subclasses: large, medium, small; three LDL subclasses: intermediate density lipoprotein (IDL), large, small; and three HDL subclasses: large, medium, small) were measured using the Vantera Clinical Analyzer (LabCorp, Burlington, NC, USA) [18, 19]. Methodology for determination of GlycA, lipoprotein insulin resistance (LP-IR) index, lipoprotein subclasses concentrations, their lipid levels and average sizes was performed using the LipoProfile-3 algorithm (LabCorp, Burlington, NC, USA) as described previously [18–20]. Lipid concentration estimates (e.g. triglycerides, VLDL triglycerides, total cholesterol, LDL-C, and HDL-C) were derived from NMR subclass particle numbers as previously described using the LipoProfile-3 algorithm [19]. Lipoprotein subclasses were also measured using the LipoProfile-4 NMR MetaboProfile algorithm [21–23]; however, as this is still considered an investigational method, results are reported as Supplemental Information.

Statistical Analysis

This secondary analysis assessing for differences between treatment arms was performed using a per-protocol 2-way repeated measures analysis of covariance (ANCOVA), with pre- and post-levels as the repeated measure, accounting for age and sex as covariates. Two-sided significance tests were performed for all analyses. Data were transformed as necessary (see Table 2) to maintain assumptions of normality. SPSS v25.0 (IBM Corp, Armonk, NY) was used for all statistical analyses. Given the exploratory nature of this study, no correction for multiple comparisons was applied, and nominal $p<0.05$ was considered significant.

Results

Following initial assessment, 40 adults were randomized to study medication, 21 to colchicine and 19 to placebo. Three subjects randomized to colchicine were withdrawn prior to study completion, so their end-study data were not included in this secondary analysis. Baseline demographic, anthropometric, inflammatory, and metabolic characteristics were similar between groups [Table 1]. At baseline, 35% of subjects (22% [n=4] colchicine vs 37% [n=7] placebo) had abnormally high triglycerides and 65% (50% [n=9] colchicine vs 58% [n=11] placebo) had abnormally low HDL-C as part of their diagnosis of metabolic syndrome. 72% (n=13) of colchicine subjects and 74% (n=14) of placebo subjects had an LDL-C concentration greater 100 mg/dL. Among the lipoprotein variables examined [Table 2], none were significantly different between groups at baseline.

As previously described [11], inflammatory markers hsCRP (p=0.0001) and erythrocyte sedimentation rate (ESR) (p=0.004) were significantly reduced by colchicine treatment [Table 2]. Similarly, colchicine treatment also significantly reduced GlycA as compared to placebo (p=0.0007). However, no significant difference in the LP-IR index was seen between groups.

At the end of the study, changes in oxLDL were significantly greater in the colchicine arm as compared to placebo (p=0.019). Colchicine also significantly increased small LDL-P concentrations (p=0.022), with no effects on medium, large, or total LDL-P. No significant colchicine-associated changes were seen for VLDL or HDL particles subclasses or for mean lipoprotein particle sizes for VLDL, LDL, and HDL [Table 2]. Additionally, no significant differences between groups were seen for changes in the common lipid parameters VLDL-C, LDL-C, HDL-C, total cholesterol, or TG (p's>0.05). Using the LipoProfile-4 algorithm, no significant changes in any of the NMR lipoprotein particle numbers or sizes, including small LDL-P, were seen between treatment arms [Supplemental Table 1].

Discussion

Several recent studies have suggested that colchicine may have cardioprotective benefits both in acute as well as in chronic CVD [5–7]. Moreover, a 2016 Cochrane systematic review found that chronic colchicine use was associated with a reduced risk of myocardial infarction, with a relative risk ratio of 0.20 (95% CI 0.07 to 0.57), although these results were heavily influenced by a single study [3]. Consequently, several large multi-center clinical trials to evaluate colchicine's effects on acute and stable CVD are currently underway [24].

However, the mechanisms behind colchicine's cardioprotective effects have not been fully elucidated. Colchicine is best known as an anti-inflammatory medication. By impairing microtubule formation and propagation, colchicine impairs leukocyte locomotion and diapedesis, inflammasome formation, and cytokine production [1, 25]. Multiple studies have demonstrated colchicine's anti-inflammatory effects in stable [9, 26], as well as acute [8], coronary artery disease. In addition to suppressing systemic inflammation, colchicine has specifically been shown to reduce vascular inflammation [10, 27, 28].

As increased concentrations of circulating inflammatory biomarkers, such as CRP, IL-6, or TNF-α, have been associated with increased risk of future CV events [29, 30], other anti-inflammatory agents have been investigated for potential CV risk reduction as well. Statins, in addition to their LDL-cholesterol lowering effect, are well-known to have anti-inflammatory properties [31]. Indeed, the JUPITER trial demonstrated that rosuvastatin reduced CV risk and all-cause mortality in at-risk individuals with elevated CRP at baseline, even if LDL-C were already low to begin with [32]. In the CANTOS trial, canakinumab, a monoclonal antibody targeting IL-1β, reduced incident CV events as compared to placebo [33]. Moreover, those individuals on treatment with CRP reduction below 2 mg/L had significant reductions in cardiovascular and all-cause mortality CV event rate as compared to those who did not achieve CRP less than 2 mg/L [34].

Secondary analyses of the CANTOS trial found that IL-6 and IL-18 levels were significant predictors of recurrent cardiovascular events and represent “residual inflammatory risk” after targeted IL-1β inhibition [35]. These results lend credence to colchicine’s potential as a cardioprotective medication. By inhibiting activation of the NLRP3 inflammasome, colchicine blocks conversion of both pro-IL-1 and pro-IL-18 to their activated states, thereby suppressing the inflammatory cascade at an “upstream” point in the pathway.

In this pilot study, colchicine successfully reduced hsCRP and ESR concentrations, as published previously [11]. However, to our knowledge, this is the first study to show that colchicine also significantly reduced GlycA concentrations, a composite NMR biomarker of systemic inflammation. The GlycA signal in NMR spectroscopy arises largely from *N*-acetyl methyl group protons of acute phase proteins and is associated with concentrations of other inflammatory biomarkers such as hsCRP, IL-6, and TNF-α [36]. GlycA has been shown to be associated with coronary artery disease burden [37] and CV disease risk even after accounting for hsCRP [38, 39]. Interestingly, GlycA has also been shown to be associated with incident T2D after adjusting for other risk factors [40, 41].

We hypothesized that colchicine’s anti-inflammatory effects would lead to a reduction in LDL oxidation and therefore reduced oxLDL concentrations. Oxidized LDL is a particularly atherogenic lipoprotein and well-known to stimulate vascular inflammation. Upon traversing the endothelial layer, oxLDL promotes nuclear factor κB (NF-κB) activation, macrophage recruitment, adhesion molecule expression, and eventually atheroma formation [42, 43]. However, surprisingly our results suggest that colchicine in fact may *increase* circulating oxLDL levels. While this seems paradoxical at first, several mechanisms may be at play. OxLDL is removed from circulation most commonly by binding to scavenger receptors, including Lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1) found prominently in endothelial cells [42]. Colchicine could be inhibiting LOX-1 translocation to the cell surface, thereby protecting against endothelial oxLDL uptake. Alternatively, colchicine may prevent macrophage scavenging of oxLDL, thereby evading vascular inflammatory activation. Further research is warranted to evaluate whether colchicine use does indeed increase oxLDL levels, and if so, the mechanisms behind this association.

As microtubules are ubiquitous and play many roles within the body, colchicine may have other CVD-protective mechanisms that should not be overlooked. Studies in rats demonstrated that microtubules are necessary for normal VLDL secretion from hepatocytes, and colchicine is able to impede this process [13, 44]. Additionally, microtubules play an important role in triglyceride and micelle translocation from the intestinal lumen to the basolateral membrane [14, 15, 45]. Taken together these studies suggested that colchicine might have the potential to lower concentrations of circulating atherogenic lipoprotein subfractions.

However, the results from this pilot randomized controlled trial indicate that colchicine, administered for three months does not significantly decrease atherogenic lipoprotein subfraction concentrations in adults with obesity and MetS. Small LDL-P, a potentially atherogenic lipoprotein subclass [46, 47], was numerically increased in the colchicine arm with a nominally significant p-value, although this result would not remain significant after

correction for the multiple comparisons performed in this study. As this investigation was a pilot study, it is always possible that findings were a result of either Type I or Type II error, and it is necessary to confirm these findings in studies with larger sample sizes.

Strengths of this study include the prospective, randomized, double-blind, placebo-controlled trial design. Adjustment for potentially confounding variables was performed in the statistical analyses. A limitation of the study was the small sample size, which may have precluded the ability to see statistically significant effects from colchicine on lipoprotein subfractions. Additionally, the subjects under study met at least 3 criteria for metabolic syndrome, rather than being restricted to those who had hypercholesterolemia or established CVD. It is possible that a study of more metabolically-unhealthy patients would find greater differences between placebo and colchicine.

In conclusion, results from this pilot study do not suggest that chronic colchicine use reduces concentrations of atherogenic lipoprotein subfractions in adults with MetS. Rather, increased concentrations of oxLDL and small LDL-P were observed in the colchicine arm. As this is an unexpected result, further studies in larger cohorts are needed to confirm these findings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Declaration of interest

APD, SRW, AW, JAL, AVS, SMB, and AR have nothing to declare. JAY receives grant support for unrelated studies sponsored by Rhythm Pharmaceuticals, Inc. using setmelanotide in people with rare syndromes causing obesity and by Soleno Therapeutics Inc. using diazoxide choline controlled release in people with the Prader-Willi syndrome.

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Table 1:

Participant Characteristics.

Data used for this secondary analysis are reported as mean ± SD except where otherwise indicated. There were no significant differences between groups for any variable listed.

Variable	Colchicine (n=18)	Placebo (n=19)
Age (y)	48.4 ± 13.5	44.4 ± 10.0
Race (n, %)		
Black	5, 28%	5, 26%
Non-black	15, 71%	14, 74%
Sex (female; n, %)	13, 72%	15, 79%
Height (cm)	168.5 ± 9.6	167.2 ± 8.2
Weight (kg)	112.3 ± 21.8	119.7 ± 31.2
Body mass index (kg/m2)	39.4 ± 6.5	42.5 ± 8.5
Body fat (%)	48.3 ± 4.0	49.0 ± 5.9
HOMA-IR	6.7 ± 3.0	6.0 ± 2.7
Hemoglobin A1c (%)	5.6 ± 0.4	5.5 ± 0.5

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Table 2:

Results.

Data are reported as unadjusted means±SD.

	Colchicine		Placebo		p value for:		
Variable	**Pre (n=18)**	**Post (n=18)**	**Pre (n=19)**	**Post (n=19)**	**Time**	**Group**	**Time*Group Interaction**
Inflammatory							
hsCRP (mg/L)	7.5±7.8	3.0±1.9	6.7±4.2	8.7±8.1	0.23	0.027	0.0001
ESR (mm/h)	17.4±12.1	10.9±7.4	21.0±12.8	21.6±12.0	0.93	0.10	0.004
GlycA (μmol/L)	424.5±62.3	393.1±60.5	422.1±39.7	438.3±37.5	0.63	0.32	0.0007
Insulin Resistance							
Lipoprotein Insulin Resistance Index	59.7±23.8	59.5±16.2	60.4±21.2	62.7±22.3	0.82	0.76	0.69
Lipoprotein Parameters							
VLDL Particles (nmol/L)							
Total VLDL-P≠	39.7±18.6	47.9±24.3	46.3±32.5	43.6±34.4	0.38	0.83	0.27
Large VLDL-P (>60nm)≠	6.1±5.0	6.4±4.1	6.8±4.7	7.7±6.0	0.026	0.65	0.77
Medium VLDL-P (35–60nm)≠	11.5±9.7	12.2±11.0	16.7±17.0	14.2±14.6	0.30	0.69	0.81
Small VLDL-P (27–35nm)≠	23.5±14.5	30.3±16.6	24.3±20.9	23.2±24.2	0.45	0.49	0.092
LDL Particles (nmol/L)							
Total LDL-P	1182.3±402.1	1239.2±400.4	1343.2±284.4	1331.1±253.3	0.79	0.17	0.41
IDL-P (23–27nm)	205.4±104.9	167.9±106.1	242.5±152.0	234.3±183.7	0.43	0.10	0.51
Large LDL-P (21.2–23nm)	461.7±246.1	462.8±236.9	450.9±285.0	465.6±289.2	0.13	0.99	0.88
Small LDL-P (18–21.2nm)≠	389.6±292.2	477.4±289.6	502.8±245.4	485.7±275.4	0.85	0.35	0.022
HDL Particles (nmol/L)							
Total HDL-P	32.7±3.2	32.3±4.5	30.6±5.2	31.1±5.4	0.35	0.43	0.29
Large HDL-P (9.4–14nm)	4.6±2.7	4.9±3.1	4.0±2.0	4.2±2.4	0.13	0.51	0.99
Medium HDL-P (8.2–9.4nm)≠	8.6±5.0	8.8±7.5	9.2±6.3	9.2±5.1	0.69	0.69	0.6
Small HDLP (7.3–8.2nm)≠	19.1±4.9	18.1±6.4	16.9±4.4	17.2±5.7	0.93	0.52	0.3
Mean Particle Size (nm)							
VLDL	53.5±10.2	52.6±7.9	53.4±9.5	55.4±9.5	0.46	0.71	0.25
LDL	21.0±0.6	20.8±0.7	20.8±0.8	20.9±0.8	0.078	0.80	0.077

	Colchicine		Placebo		p value for:		
Variable	**Pre (n=18)**	**Post (n=18)**	**Pre (n=19)**	**Post (n=19)**	**Time**	**Group**	**Time*Group Interaction**
HDL	9.0±0.4	9.0±0.5	9.0±0.3	9.0±0.4	0.021	0.62	0.98
Derived Concentrations (mg/dL)							
Total Triglycerides	117.7±50.9	125.0±53.5	131.8±57.7	135.3±66.1	0.59	0.51	0.87
VLDL Triglycerides[≠]	78.4±43.0	84.5±45.1	86.7±51.5	90.3±58.6	0.19	0.99	0.76
Total Cholesterol	172.7±36.2	175.9±37.6	183.3±35.6	175.9±34.8	0.72	0.27	0.77
LDL-C	112.4±34.7	113.1±35.0	124.6±33.2	123.9±29.2	0.84	0.16	0.94
HDL-C	50.3±10.3	50.2±11.5	47.5±9.0	47.2±10.9	0.23	0.53	0.84
Other							
oxLDL (U/L)[≠]	70.0±25.6	74.3±19.1	78.0±20.7	69.3±15.4	0.99	0.54	0.019

[≠]Untransformed Pre and Post data are shown for clarity even though the data required transformation for the statistical analysis of these variables.