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Review

The effects of a nutraceutical combination on plasma lipids and glucose: A systematic review and *meta*-analysis of randomized controlled trials

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ABSTRACT

Dyslipidemia and hyperglycemia are associated with an increased risk of ischemic cardiovascular disease. Positive effects of a nutraceutical combination comprising red yeast rice, berberine, policosanol, astaxanthin, coenzyme Q_{10} and folic acid (NComb) on plasma lipid and glucose levels have been reported in some but not all clinical trials. To address this inconsistency, we tried to estimate the size of lipid- and glucose-lowering effects of NComb through a systematic review and *meta*-analysis of randomized controlled trials.

A systematic literature search in PubMed-Medline, SCOPUS and Google Scholar databases was conducted to identify randomized controlled trials investigating the effects of NComb on plasma lipids and glucose levels. Inverse variance-weighted mean differences (WMDs) and 95% confidence intervals (CIs) were calculated for net changes in lipid and glucose levels using a random-effects model. Random-effects *meta*-regression was performed to assess the effect of putative confounders on plasma lipid and glucose levels.

Fourteen trials (1670 subjects in the NComb arm and 1489 subjects in the control arm) met the eligibility criteria for lipid analysis and 10 trials (1014 subjects in the NComb arm and 962 subjects in the control arm) for glucose analysis. Overall, WMDs were significant for the impact of NComb supplementation on plasma levels of total cholesterol (−26.15 mg/dL, $p < 0.001$), LDL-cholesterol (−23.85 mg/dL, $p < 0.001$), HDL-cholesterol (2.53 mg/dL, $p < 0.001$), triglycerides (−13.83 mg/dL, $p < 0.001$) and glucose (−2.59 mg/dL, $p = 0.010$). NComb-induced amelioration of lipid profile was not affected by duration of supplementation nor by baseline lipid levels; conversely, a greater glucose-lowering effect of NComb was found with higher baseline glucose levels and longer durations of supplementation.

In conclusion, the present results suggest that NComb supplementation is associated with improvement of lipid and glucose profile. Short-term beneficial effects of NComb supplementation appear to be maintained in the long term.

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Abbreviations: SX, astaxanthin; BBR, berberine; BMI, body mass index; CIs, confidence intervals; CMA, comprehensive *meta*-analysis; CoQ_{10}, coenzyme Q_{10}; CVD, cardiovascular disease; FA, folic acid; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; NComb, nutraceutical combination; PCS, policosanol; RCTs, randomized controlled trials; RYR, red yeast rice; SD, standard deviation; WMD, weighted mean difference.

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Contents

1. Introduction

Dyslipidemias and hyperglycemia are established risk factors for ischemic cardiovascular disease (CVD) [1,2]. There is a consistent relationship between most of the dyslipidemic phenotypes, such as hypercholesterolemia, hypertriglyceridemia and hypoalphalipoproteinemia, and the risk of CVD [3,4]. The combination of multiple lipid fraction abnormalities is common [5] and shows a detrimental cumulative impact on CVD risk [1].

Similar to dyslipidemias, hyperglycemia *per se* has a negative impact on CVD risk [2,5], and glucose levels in the diabetic range are associated with an increased CV mortality [6]. The association between fasting blood glucose and CVD burden has also been demonstrated in non-diabetic [1,7].

The association of dyslipidemia and hyperglycemia, that are inter-related through a mechanistic link where insulin-resistance is involved as a prominent primer, further aggravates their detrimental prognostic significance [8].

Given the alarmingly high prevalence and unfavourable coexistence of lipid and glucose abnormalities on the one hand [9,10], and the time-dependent relationship between exposure to these conditions and vascular risk on the other [11,12], lipid- and glucose-lowering strategies have been proposed to be initiated early before CVD appearance [13,14].

A quite novel approach, at least in Western countries, to treat dyslipidemias and hyperglycemia involves the use of nutraceuticals [15]. Cholesterol-lowering effects of red yeast rice (RYR) and berberine (BBR), administered as single agents, have been confirmed in some *meta*-analyses of randomized controlled trials (RCTs) [16,17]. Also, the glucose-lowering effect of BBR has been demonstrated along with the evidence for a potential triglyceride-lowering effect [17]. The role of policosanol (PCS) in reducing cholesterol is controversial and far to be confirmed in studies outside Cuba [18]. Finally, astaxanthin (ASX) and coenzyme Q_{10} (CoQ_{10}) have demonstrated variable effects on plasma lipids and glucose levels [19–23]. Hence, the possibility to exploit combined lipid- and glucose-lowering effects of multiple nutraceuticals has led to the development of specific nutraceutical combinations [15,24].

Nutraceutical combinations have been used as therapeutic strategies especially for those patients whose lipid and glucose levels were marginally high but not enough to warrant the prescription of either lipid- or glucose-lowering medications [15,24]. A specific low-dose combination of nutraceuticals (NComb), containing RYR, BBR, PCS, ASX, CoQ_{10} and folic acid (FA) has been reported to be effective in reducing total and low-density lipoprotein (LDL) cholesterol levels in most [25–37] but not all trials [38]. The magnitude of cholesterol reduction using NComb, and its influence on plasma triglycerides, high-density lipoprotein (HDL) cholesterol and glucose levels varied across trials, which could be partly atrtibuted to the variable durations and sample sizes of trials exploring lipid- and glucose-lowering effects of NComb.

Despite combination of lipid- and glucose-lowering nutraceuticals like RYR, BBR, PCS, ASX and CoQ_{10} seems attractive to target patients with mild dyslipidemias and hyperglycemia in their early stages, there is substantial uncertainty about the net effect of this NComb on plasma lipid and glucose levels. The present study aimed to explore this uncertainty through a systematic review and *meta*-analysis of clinical trials investigating the effects of NComb on plasma lipid and glucose levels.

2. Methods

2.1. Search strategy

This study was designed according to the guidelines of the 2009 preferred reporting items for systematic reviews and *meta*-analysis (PRISMA) statement [39]. PubMed-Medline and SCOPUS databases were searched using the following search terms in titles and abstracts: ("cholesterol" OR "LDL" OR "HDL" OR "triglyceride" OR "glucose" OR "glycemia") AND ("red yeast rice" OR "monacolin" OR "armolipid"). Also, the following search terms were used in Google Scholar: (cholesterol AND berberine AND policosanol AND nutraceutical). The wild-card term "*" was used to increase the sensitivity of the search strategy. The search was limited to articles published in English language. The literature was searched from inception to February 10, 2016.

2.2. Study selection

Original studies were included if they met the following inclusion criteria: (i) being a clinical trial with either parallel or cross-over design, (ii) investigating the impact of low-dose NComb [RYR extract 200 mg (equivalent to 3 mg monacolin), BBR 500 mg, PCS 10 mg, ASX 0.5 mg, CoQ_{10} 2 mg and FA 0.2 mg] on serum/plasma concentrations of total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides or glucose, (iii) presentation of sufficient information on lipid an glucose concentrations at baseline and at the end of follow-up in each group or providing the net change values. Exclusion criteria were (i) non-interventional studies, (ii) uncontrolled studies, and (iii) observational studies with case-control, cross-sectional or cohort design.

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