Original article

Effect of resistant starch supplementation on blood lipids in metabolic disorder adults: A meta analysis of randomized controlled trials

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Received May 28, 2019; Accepted August 17, 2019

Resistant starch (RS) acts as insoluble fiber and by definition is resistant to enzymatic digestion in the small intestine and is non-viscous. The results of randomized controlled trials (RCTs) investigated that resistant starch(RS) supplementation on the effect of blood lipids in metabolic disorder adults have been inconsistent. The present meta-analysis aimed to quantitatively evaluate the effect of RS intervention on the concentration of blood lipids. PubMed, Cochrane, and Web of Science databases were searched up to July 2019. Mean differences were calculated on the effect of lipids by using a random-effects model. Pre-specified subgroup analyses were carried out to explore the sources of heterogeneity. Six studies (10 treatment arms) with 320 participants were identified. The result showed that RS supplementation had no significant effect on concentration of TC (-0.28 mmol/L, 95% CI: -0.68 to 0.12 mmol/L, $P=0.16$, $I^2=94\%$), TG (-0.42 mmol/L, 95% CI: -1.02 to 0.19 mmol/L, $P=0.18$, $I^2=99\%$), HDL (0.06 mmol/L, 95% CI: -0.15 to 0.27 mmol/L, $P=0.57$, $I^2=96\%$) and LDL(-0.17 mmol/L, 95% CI: -0.70 to 0.37 mmol/L, $P=0.54$, $I^2=94\%$). Subgroup analysis showed that there were decreased effect on TC concentration when RS was less than or equal to 30 g, but increased effect on TG and LDL concentration when the dose of RS was more than 30 g, and increased effect on TG in people who were overweight; no significant effect on HDL concentration no matter the dose of RS, the intervention time or the disorder status of people.

Key Words: Resistant starch; Blood lipids; Meta analysis; Randomized controlled trials

INTRODUCTION

Resistant starch (RS) acts as insoluble fiber and by definition is resistant to enzymatic digestion in the small intestine and is non-viscous, but could be fermented and utilized by the microbiota in the colon.¹ RS is classified into five subtypes (RS1-RS5), namely physically trapped starch, resistant starch granules, retrograded starch, chemically modified starch, and amylose-lipid complexes.² Like other insoluble fibers, it is fermented in the colon by the microflora which releases carbon dioxide, methane, hydrogen and metabolically active short chain fatty acids (primarily acetate, propionate and butyrate) which are utilized by the colonic epithelium and enter the portal circulation.³

In the past several years, there has been continued interest in the

physiological effects of resistant starch, since it might be an attractive source of non-caloric food with a more palatable character than insoluble dietary fiber. It is generally accepted that

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How to cite this article: Miao TT, Yu Y, Hu HT, Sun J, Cui MJ, Ma AG, Zhang MY. Effect of resistant starch supplementation on blood lipids in metabolic disorder adults: A meta analysis of randomized controlled trials. *J ADV HEALTH* 2019; 1(4): 70-84.

RS replaced for digestible starch in the diet can lower serum cholesterol concentrations in normal or hypercholesterolemic conditions in animals.⁴⁻¹⁰ However, in humans, these findings are not yet fully supported. For example, the cholesterol lowering effect has not been found with normolipidemic subjects.¹¹ Also, postprandial cholesterol lowering effect was not observed with RS supplementation in healthy adults, even though there was a decrease in postprandial TG concentration.¹² It has been proposed that the cholesterol-lowering effect observed in animal models is attributed to the increased production of short-chain fatty acids (SCFA) in the large intestine. In human studies, a general rise in SCFA was often examined,^{13,14} however, there is no conclusive evidence that this is related to blood lipids performance.

Recently, several RCTs regarding RS supplementation on the effect of blood lipids have been published; however, the results are still inconsistent. In addition, there has been no meta-analysis of this matter so far. Therefore, to provide a more comprehensive, up-to-date assessment of RS supplementation, we conducted a meta analysis of RS supplementation on effects of blood lipids.

METHODS

Design

The study was designed in accordance with the Cochrane Handbook for Systematic Reviews of Interventions.¹⁵ We reported our results according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement.¹⁶ Two investigators (Tingting Miao and Yun Yu) independently performed the literature search, study selection, data extraction, and methodologic quality assessment. The disagreement was resolved in consultation with a third investigator (Haiting Hu).

Literature search

A systematic literature search was conducted in PubMed, Cochrane, and Web of Science databases up to July 2019. We used “Starch/analogs and derivatives” [Mesh], resistant starch, Non-digestible starch, high amylose starch, fiber, “Lipids/blood” [Mesh], Triglycerides, triacylglycerol, cholesterol, lipid, low density lipoprotein, high density lipoprotein and “Clinical Study” [Publication Type] NOT “Observational Study” [Publication Type] OR random as search terms. Additionally, reference lists of original studies, recent reviews, and meta-analyses were also scrutinized. Clinical trials with resistant starch as intervention were included. The metabolic disorder enrolled volunteers were type 2 diabetes, overweight, and metabolic syndrome adults. A study that met the following criteria was included in the meta-analysis: ① RCTs of either parallel or cross-over design; ② the study assessed the impact of RS or standardized resistant starch-enriched carbohydrate on effect of blood lipids; ③ the study had an appropriate controlled design, e.g., if RS was administrated as an adjunct to another supplement, the control group received another carbohydrate supplement; and ④ the study provided available data to calculate the differences between baseline and endpoint on effect of blood lipids.

Data extraction

Predefined data were extracted from each report with the use of standardized forms. We extracted information on literature

characteristics, such as the first author, publication year, country, sample-size, gender, mean age, health status, duration of intervention, study design, the dose of RS and control intake per day. Besides, the means and standard deviations (SDs) of TC, TG, HDL, and LDL at the endpoint in both intervention and control groups were extracted, respectively. The Cochrane score criteria were used for quality assessment, including the following items: ① random sequence generation, ② allocation concealment, ③ blinding of participants and personnel, ④ blinding of outcome assessment, ⑤ incomplete outcome data, ⑥ selective reporting. The units were converted to mmol/L for blood lipids.

Data synthesis

A random-effects model was employed to calculate the pooled estimates. Heterogeneity between the studies was evaluated by I^2 statistic. The I^2 values of 25%, 50%, and 75% were classified as low, moderate, and high degrees of heterogeneity, respectively.¹⁶ To identify the source of heterogeneity, subgroup analyses were performed to focus on information of the subjects: the dose of RS supplementation, duration of intervention, and disorder status of subjects. Statistical analysis was performed with RevMan5.3 software. Except as otherwise specified, $P < 0.05$ was considered as statistically significant.

RESULTS

Results of study selection

The flow diagram of the literature search was shown in Figure 1. After the removal of 2736 duplicates, 3716 unique articles were retrieved. Of these, 3569 articles were deleted by screening the titles and abstracts, leaving 147 articles for full-text examination. After checking full-text, 141 articles were excluded because they did not meet the inclusive criteria (e.g., without providing available data, multi-component intervention, and study design). Ultimately, 6 articles were selected for inclusion and quantitative synthesis.

Figure 1 Flow diagram of the study selection procedure

Study characteristics

The characteristics of the 6 articles are shown in Table 1.

Among them, 3 studies were conducted in UK (Bodinham et al., 2014; Robertson, et al., 2012; Bodinham et al., 2012), 2 in Asia (Gargari et al., 2015; Zhang et al., 2007), 1 in Oceania (Noakes et al., 1996). The sample-size of the subjects ranged from 12 to 60, with a total of 320 participants. The dose of RS supplementation ranged

Table 1 The Characteristics of the 6 eligible RCTs

Author' Year	Country	No. (In- tervention/co ntrol)	Gender(F/M); age	Duration (intervention/ washout)	People	Intervention	Control	outcome	Study design
Bodinham, 2014	UK	17(17/17)	(5/12); 55±2.4	12weeks/ 12weeks	type 2 diabetes	RS ¹ (80g)+ RDS ² (54g)	RS2(0g)+RDS(54g)	TG ⁴ , TC ⁵ , HDL ⁶ , LDL ⁷	crossover
Bodinham, 2012	UK	12(12/12)	(4/8); 37±4.0	4 weeks/ 4 weeks	overweight people	RS2(40g)+ RDS(27g)	RS2(0g)+RDS(27g)	TG, TC	crossover
Gargari, 2015	Iran	60(28/32)	(60/0); Control:49.6 (8.4), Intervention: 49.5 (8.0)	8 weeks	type 2 diabetes	RS2(10g)	maltodextrin(10g)	TG, TC, HDL, LDL	parallel
Zhang, 2007	China	40(20/20)	(23/17); 51.1±7.9/ 52.2±11.1	4 weeks/ 1 week	type 2 diabetes	RS ³ (30g)	wheat flour (30g)	TG, TC	crossover
Noakes, 1996	Australia	23(23/23)	(10/13); 44-64	4 weeks/ 0 week	overweight people	RS(30g for women/ 44.4g for men)	Oat bran(87/121g), low amylose starch (11-13g)	TG, TC, HDL, LDL	crossover
Robertson, 2012	UK	15(15/15)	(7/8); 48.9±3.9	8 weeks/ 8 weeks	overweight people	RS2(40g)+ RDS(27g)	RS2(0g)+ RDS(27g)	TG, TC	crossover

¹RS2, type 2 resistant starch derived from high amylose maize; ²RDS, rapidly digestible starch; ³RS, resistant starch; ⁴TC, total cholesterol; ⁵TG, triglyceride;

⁶HDL, high-density lipoprotein; ⁷LDL, low density lipoprotein.

from 10 to 80 g, and the duration of intervention lasted from 4 weeks to 12 weeks. One study has reported the different doses of RS for men and women, respectively (Noakes et al., 1996). Three studies were conducted in metabolic disorder subjects, including two studies with overweight subjects and one study with metabolic syndrome adults. Three studies were conducted in subjects with type 2 diabetes (T2DM). Five studies used cross-over design and one study used parallel design.

Quality assessment

The quality assessment of each study was conducted by the Cochrane Bias risk assessment [Figure 2]. Incomplete outcome data (attrition bias) and selective reporting (reporting bias) showed low risk, while random sequence generation (selection bias) and allocation concealment (selection bias) showed low risk partially with mostly unclear risk. However, blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), and other bias showed low, unclear, high risk overall.

Figure 2 Quality assessment of the included studies

Effect of RS on blood lipids

Effect of RS on TC

All the trials provided available data on TC. The result showed that RS supplementation had no significant effect on TC concentration (-0.28 mmol/L; 95% CI: -0.68 to 0.12 mmol/L; $P=0.16$), with a high between-study heterogeneity ($I^2=94\%$) [Figure 3]. Therefore, the subgroup analysis could be conducted for further analysis.

Figure 3 Effect of RS intervention on TC concentrations

Effect of RS on TG

All the trials provided available data on TG. The result showed that RS supplementation had no significant effect on TG

concentration (-0.42 mmol/L, 95% CI: -1.02 to 0.19 mmol/L, $P=0.18$), with a high between-study heterogeneity ($I^2=99\%$) [Figure 4]. Therefore, the subgroup analysis could be conducted for further analysis.

Figure 4 Effect of RS intervention on TG concentrations

Effect of RS on HDL

There are three studies containing six trails that provided available data on HDL. The result showed that RS supplementation had no

significant effect on HDL concentration (0.06 mmol/L, 95% CI: -0.15 to 0.27 mmol/L, $P=0.57$), with a high between-study heterogeneity ($I^2=96\%$) [Figure 5]. Therefore, the subgroup analysis could be conducted for further analysis.

Figure 5 Effect of RS intervention on HDL concentrations

Effect of RS on LDL

There are three studies containing six trails that provided available data on LDL. The result showed that RS supplementation had no

significant effect on LDL concentration (-0.17 mmol/L, 95% CI: -0.70 to 0.37 mmol/L, $P=0.54$), with a high between-study heterogeneity ($I^2=94\%$) [Figure 6]. Therefore, the subgroup analysis could be conducted for further analysis.

Figure 6 Effect of RS intervention on LDL concentrations

Subgroup analysis

To explore the sources of heterogeneity, subgroup analyses were conducted. For the included studies, the dose of RS supplementation, duration and disorder status were different, which may be the sources of heterogeneity, because differences in the dose and type of RS, duration of intervention, basal

inflammatory/anti-inflammatory status, different comparison, ethnicity, and genotype may result on the contrary results.¹³ We used a dose of resistant starch of 30 g as the cutoff, and the results showed that the supplemental RS reduced the concentrations of TC (-0.63 mmol/L, 95% CI: -1.21, -0.04; $I^2=84\%$, $P=0.04$) when the dose is less than or equal to 30g, while increased the concentrations of TG (0.21mmol/L, 95% CI: 0.15, 0.26; $I^2=0\%$,

$P < 0.00001$), LDL (0.10 mmol/L, 95% CI: 0.03, 0.16; $I^2 = 0\%$, $P = 0.005$) when the dose is more than 30 g. In addition, we set the disorder status as T2DM or overweight people. The results showed a

increased effect on TG (0.22 mmol/L, 95% CI: 0.12, 0.31; $I^2 = 0\%$, $P < 0.00001$) in the overweight people. There were no significant effects on other subgroups except the above results [Table 2].

Table 2 Subgroup analyses for TC, TG, HDL and LDL concentrations.

Factors stratified	TC				TG				HDL				LDL			
	No.	95% CI	Heterogeneity		No.	95% CI	Heterogeneity		No.	95% CI	Heterogeneity		No.	95% CI	Heterogeneity	
			$I^2(\%)$	P			$I^2(\%)$	P			$I^2(\%)$	P			$I^2(\%)$	P
Dose of resistant starch																
≤30 g	5	-0.63 (-1.21, -0.04)	84	0.04	5	-1.04 (-3.10, 1.02)	98	0.32	3	0.12 (-0.21, 0.46)	92	0.47	3	-0.36 (-1.18, 0.46)	82	0.39
>30 g	5	0.07 (-0.08, 0.22)	38	0.36	5	0.21 (0.15, 0.26)	0	<0.00001	3	-0.00 (-0.06, 0.05)	0	0.96	3	0.10 (0.03, 0.16)	0	0.005
Duration																
<8 weeks	7	-0.21 (-0.53, 0.11)	58	0.20	7	-0.02 (-0.42, 0.37)	69	0.91	4	-0.01 (-0.09, 0.07)	0	0.78	4	-0.01 (-0.33, 0.30)	0	0.94
≥8 weeks	3	-0.36 (-1.23, 0.50)	98	0.41	3	-1.15 (-2.39, 0.10)	100	0.07	2	0.20 (-0.19, 0.58)	99	0.32	2	-0.43 (-1.48, 0.62)	99	0.42
Type of participants																
T2DM	4	-0.70 (-1.64, 0.24)	98	0.14	4	-1.22 (-3.58, 1.14)	100	0.31	2	-0.01 (-0.09, 0.07)	0	0.78	4	-0.01 (-0.33, 0.30)	0	0.94
Overweight	6	-0.03 (-0.18, 0.12)	0	0.70	6	0.22 (0.12, 0.31)	0	<0.00001	2	0.20 (-0.19, 0.58)	99	0.32	2	-0.43 (-1.48, 0.62)	99	0.42

Abbreviations: CI, confidential interval; T2DM; type 2 diabetes mellitus.

DISCUSSION

Summary of evidence

In recent researches, some reported that RS did not lower serum lipid concentrations,^{12,18,19} while several investigators have proposed RS as a new category of dietary fiber possessing some metabolic functions against abnormality caused by an extra supply of energy or fat.²⁰⁻²⁴ Since RS remains mostly undigested until it is partially fermented in the colon, the metabolism of RS appears to occur 5-7 h after consumption in contrast to normally cooked starch which is digested almost immediately.²⁵

From the previous studies, RS played a useful role in health by some potential mechanisms include: ① changes in intestinal microbiota, ② a reduction in insulin, ③ resistance rise in HDL-c concentrations, and ④ an increase in SCFAs production.^{3-6,26-34} RS could produce SCFAs through two pathways: directly (RS fermentation) or indirectly (increasing colonic butyrate-producing microbiota such as *Lachnospiraceae* and *Ruminococcaceae*). Butyrate can control macrophage activity and expression of NF-κB which is the main inflammatory and immune response. Additionally, it can raise the expression of cytokine signaling 3 suppressors (SOCS 3), secretion of IL-10, reduce the expression of pyrogenic factors (e.g., Myeloperoxidase) and IL-12 level.³⁵ Recent research showed that butyrate could regulate the release of GLP-1 through its central and peripheral targets.^{32,34,36} However, Castillo et al. reported that consumption of native banana starch supplementation (24 g/d) as a rich source of RS2 for 4 weeks did not affect the lipid profile, HbA1c and FBS and insulin resistance in obese T2DM patients.³⁷

Therefore, it is meaningful to investigate the effect of RS on blood lipids to obtain relatively reliable evidence. However, in this meta-analysis article, RS supplementation showed no significant effects on TC, TG, HDL, and LDL with high heterogeneity. The high heterogeneity may result from the different dose of RS, different duration and disorder status, because there were some

conclusions showed that differences in the dietary intake (RS, macronutrient, total fiber), dose and type of RS, basal inflammatory/anti-inflammatory status, duration of intervention, ethnicity and genotype may result on the contrary results.¹⁷

However, we conducted a subgroup analysis to analyze the source of high heterogeneity. Data from the current meta-analysis of 6 articles (in 320 participants) showed that RS supplementation had decreased effect on TC concentration when the dose of RS was less than or equal to 30 g, but had increased effect on TG and LDL concentration when the dose of RS was more than 30 g. These results may be explained from that the RS does not seem to bind to bile acids, so the more intake may not have a significant effect on blood lipids.^{11,12} Another reason may be the limited SCFA concentrations increased by RS. Because some studies had reported that SCFA does not discount a change in fecal/luminal concentrations, which may be involved in the increased stimulation of GLP1 through the FFAR 2/3 receptor.^{32,34,38} Additionally, some researches had reported that RS2 could not improve human health as expected because of its instability by gelatinization as natural starch granules.^{31,39} The result suggested that the supplementation of RS was not useful to control blood lipids in overweight people with no drug treatment, which may be due to the shorter duration of fewer than 8 weeks. Meanwhile, it was verified RS could increase TG concentration no matter dose or duration. However, the result showed that there was no significant effect on HDL concentration no matter the dose of RS, the intervention time, or the disorder status of people.

Limitations and future research needs

The present meta-analysis provided substantial evidence of RS supplementation on blood lipids in metabolic disorder adults for the first time. However, there may be some reasons for the poor results. First, there was publication bias in the six articles, which may affect the result that we obtained. Another possible reason was that the included studies were limited because the relevant

articles were fewer, which resulted in a high heterogeneity. However, in subgroup analysis, the number of some subgroups included in the study were very few, which the results provided may not be true. Therefore, further focus on the RCTs or observation studies of RS effects on blood lipids, including the different types and more results should be conducted.

CONCLUSION

In conclusion, the results of this study showed that in metabolic disorder people, RS supplementation had decreased effect on TC concentration when the dose of RS was less than or equal to 30 g/d, but had increased effect on TG and LDL concentration when the dose of RS was more than 30 g/d, while there was no significant effect on HDL concentration no matter the dose of RS or the intervention time. However, with the limits of this meta-analysis, there will be more focus on the further researches, which are relevant to the effect of RS on blood lipids, including different type of RS in order to obtain a new viewpoint on how the supplement of RS affect the blood lipids concentration in metabolic disorder people.

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