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Review article

Effects of exercise on reverse cholesterol transport: A systemized narrative review of animal studies

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ABSTRACT

Aims: Reverse Cholesterol Transport (RCTr) is the mechanism by which excess cholesterol from peripheral tissues is transported to the liver for hepatobiliary excretion, thereby inhibiting foam cell formation and the development of atherosclerosis. Exercise affects RCTr, by influencing high-density lipoprotein cholesterol (HDL) through remodeling and by promoting hepatobiliary sterol excretion. The objectives of this systematized review of animal studies is to summarize the literature and provide an overview of the effects of chronic exercise (at least two weeks) on apolipoproteins (Apo A-I, Apo-E), Paraoxonase-1 (PON1), ATP-binding cassette transporters (ABCA1, ABCG1, ABCG4, ABCG5, ABCG8), scavenger receptor class B type I (SR-BI), cholesteryl ester transfer protein (CETP), low-density lipoprotein receptor (LDLr) and cholesterol 7 alpha-hydroxylase (CYP7A1) and Niemann-Pick C1-like 1 (NPC1L1).
Materials and methods: Three electronic databases (PubMed, Science Direct and Google Scholar) were searched for eligible studies conducted from the earliest available date to August 2018.
Key findings: Most of studies investigate the effects of low to moderate intensity aerobic training on RCTr elements. The majority were on exercised rats undertaking moderate intensity aerobic training.
Significance: This review highlights that moderate intensity and longer-term training has a greater effect on RCTr elements than low intensity training. There a few studies examining high intensity training which warrants further investigation.

1. Introduction

Cardiovascular disease (CVD) is still the leading cause of death globally [1]. A strong inverse correlation between plasma concentrations of high-density lipoprotein cholesterol (HDL) and the incidence of atherosclerotic-driven CVD has been shown previously [2,3]. This has led to the hypothesis that interventions aimed at increasing HDL levels might positively influence the risk of CVD [4,5]. The main atheroprotective function of HDL particles is via the process of Reverse Cholesterol Transport (RCTr) [6–8].

The main molecules involved in RCTr are apoliproteins (Apo A-I and Apo-E), Paraoxonase-1 (PON1), ATP-binding cassette transporters (ABCA1, ABCG1, ABCG4, ABCG5, ABCG8), scavenger receptor class B type I (SR-BI), cholesteryl ester transfer protein (CETP), low-density lipoprotein receptor (LDLr) and cholesterol 7 alpha-hydroxylase (CYP7A1) and Niemann-Pick C1-like 1 (NPC1L1) [9–11] (Fig. 1). ABCA1 transport cellular cholesterol and phospholipids to lipid-poor apolipoproteins, such as ApoA-I [12,13]. ApoA-I also triggers a reaction called cholesterol esterification that converts cholesterol to a form that can be fully integrated into HDL and transported through the bloodstream [12,14]. PON1 attracted significant interest as a protein that is responsible for the most of antioxidant properties of HDL[15]. ABCG1/G4 acts on the plasma membrane to facilitate the efflux of cellular sterols to exogenous HDL ([16,17].

Apolipoprotein E (ApoE) is a fat-binding protein that is part of the chylomicron and Intermediate-Density Lipoprotein (IDL). These are essential for the normal processing (catabolism) of triglyceride-rich lipoproteins. In peripheral tissues, ApoE is primarily produced by the liver and macrophages, and mediates cholesterol metabolism [18,19]. The scavenger receptor class B type I (SR-B1) plays an important role in meditating the uptake of HDL-derived cholesterol and cholesteryl ester in the liver and steroidogenic tissues. In addition to being ubiquitous,

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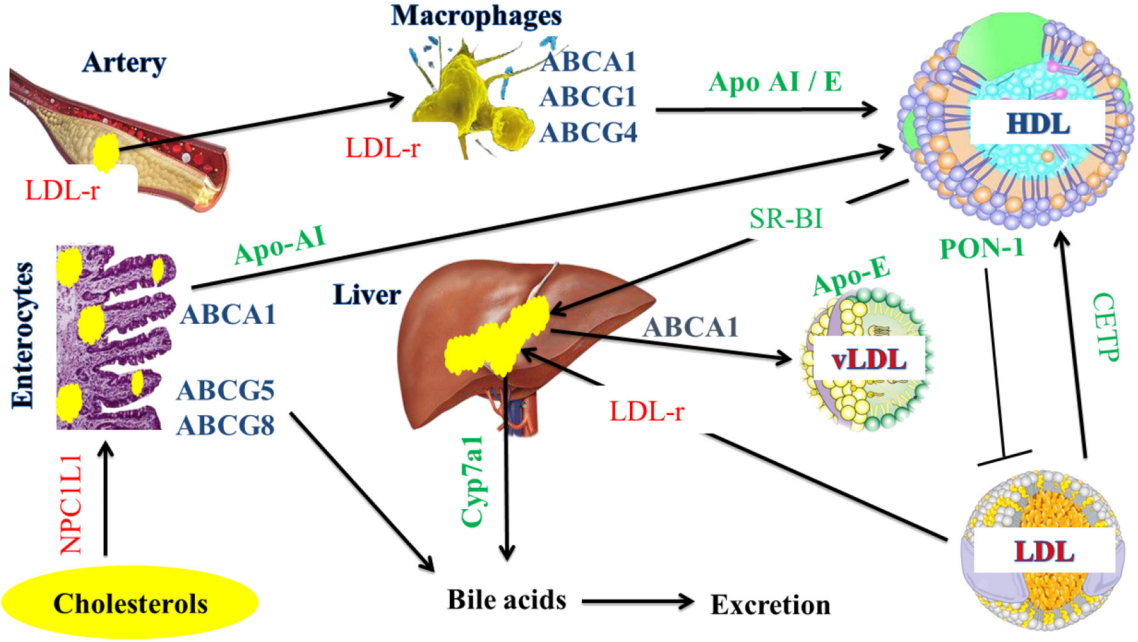

Fig. 1. Reverse cholesterol transport.
Adapted from Maqdasy et al. (2016) [31].

SR-B1 is a HDL receptor in many tissues [12,20].

Cholesteryl ester transfer protein (CETP), also called plasma lipid transfer protein, is a plasma protein that facilitates the transport of cholesteryl esters and triglycerides (TG) between the lipoproteins. It collects TG from very-low-density lipoprotein (VLDL) or low-density lipoproteins (LDL) and exchanges them for cholesteryl esters from HDL, and vice versa. However, CETP does a heteroexchange, trading a triglyceride for a cholesteryl ester or a cholesteryl ester for a triglyceride [21,22].

The Low-Density Lipoprotein Receptor (LDL-R) is a mosaic protein of 839 amino acids (after removal of 21-amino acid signal peptide) that mediates the endocytosis of cholesterol-rich LDL. It is a cell-surface receptor that recognizes the apoprotein B100, which is embedded in the outer phospholipid layer of LDL particles. The receptor also recognizes the ApoE protein found in chylomicron remnants and VLDL remnants IDL [19,23,24]. CYP7A1 has an important role in cholesterol metabolism. It is a cytochrome P450 enzyme, which belongs to the oxidoreductase class, and converts cholesterol to 7-alpha-hydroxycholesterol, the first and rate limiting step in bile acid synthesis. Hepatic G5/G8 mediates cholesterol excretion into bile. Intestinal G5/G8, limit intestinal absorption and promote biliary excretion of neutral sterols [25,26].

Niemann-Pick C1-Like 1 (NPC1L1) is a polytopic transmembrane protein localized at the apical membrane of enterocytes and the canalicular membrane of hepatocytes. It functions as a sterol transporter to mediate intestinal cholesterol absorption and counterbalances hepatobiliary cholesterol excretion [10,27]. Recent findings led to the beneficial effects of exercise on CVD [2,28,29]. Several molecular pathways and mechanisms of action affecting CVD risk have been found to be influenced by exercise, including cholesterol efflux and RCTr [2,30]. This review aims to summarize current knowledge on the effects of chronic exercise (at least two weeks) on RCTr in animal studies.

2. Methods

2.1. Data bases and keywords

Three electronic databases were searched i.e. 1) PubMed, 2) Science Direct and 3) Google Scholar for eligible studies conducted from the earliest available date to August 2018. The following keywords were used in the searches in conjunction with Medical Subject Heading (MeSH) terms, including apolipoproteins (Apo A-I and Apo-E) and exercise/training/physical activity, Paraoxonase-1 (PON1) and exercise/training/physical activity, ATP-binding cassette transporters (ABCA1, ABCG1, ABCG4, ABCG5, ABCG8) and exercise/training/physical activity, scavenger receptor class B type I (SR-BI) and exercise/training/physical activity, cholesteryl ester transfer protein (CETP) and exercise/training/physical activity, low-density lipoprotein receptor (LDLR) and exercise/training/physical activity, cholesterol 7 alpha-hydroxylase (CYP7A1) and exercise/training/physical activity, Niemann-Pick C1-like 1 (NPC1L1) and exercise/training/physical activity. After searching 23,420 articles were identified. These papers were exported to Endnote program version 7 and after the removal of duplicates 525 remained. Titles and abstracts were screened using the following inclusion criteria:

2.2. Procedural condition of Included Studies

(1) English language.
(2) An original article on animal models.
(3) The training intervention duration had to be at least 2 weeks.

3. Results

After full text screening, 41 papers were included in this review. The total number and flow of articles identified from electronic searching databases is shownin Fig. 2.

The following sections provides a summary of the main findings of the identified molecules. Comprehensive details of the animal, exercise training protocol and results for each of the studies used in this review can be found in Table 1.

3.1. ApoA-I

de Moraes et al. (2008) showed that aerobic exercise increases apolipoprotein A-I expression in the rabbit renal cortex [33]. Khabazian et al. (2009) found endurance training enhances plasma apoA-I in rats [34]. Bouwman et al. (2010) highlighted that endurance training

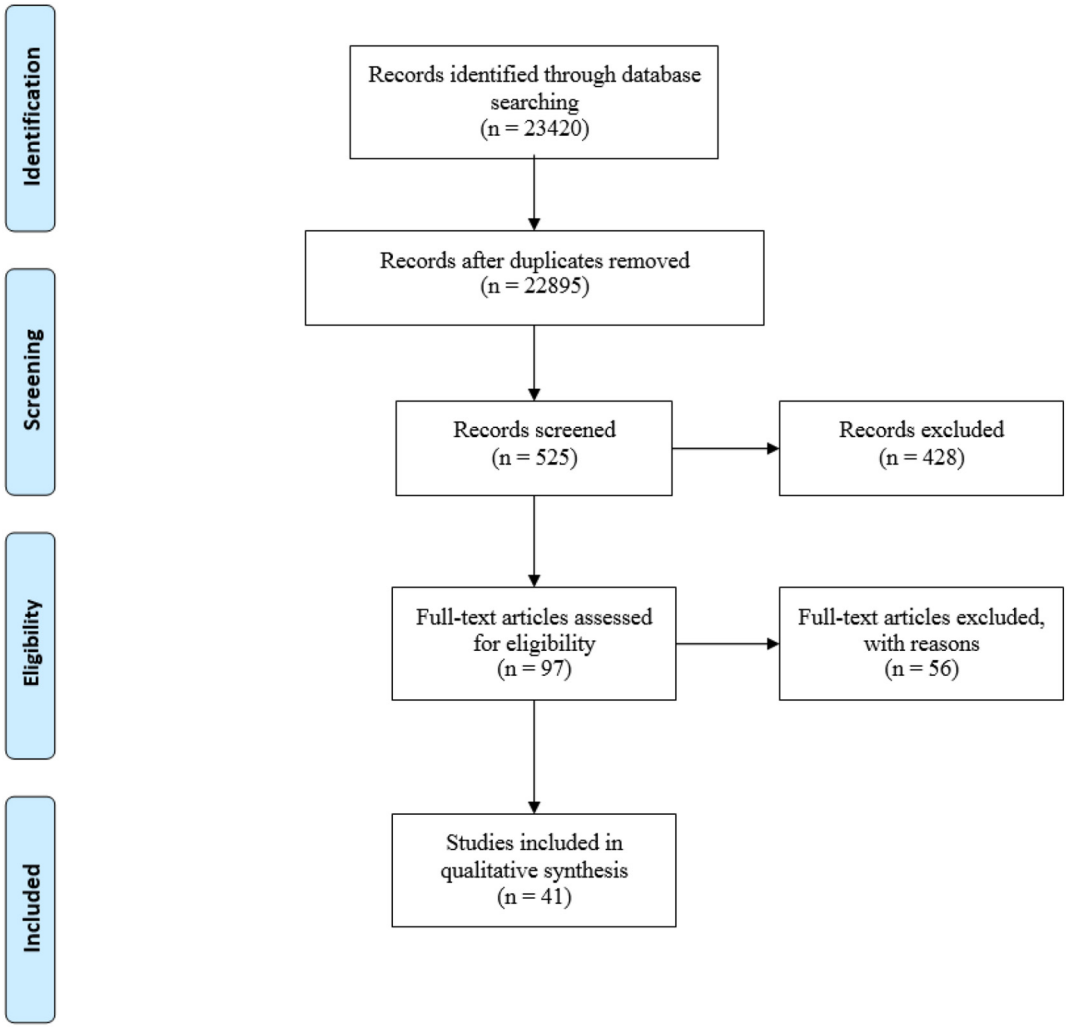

Fig. 2. Results of database searching on the basis of PRISMA Group (2009) [32].

enhances apoA-I expression in vastus lateralis muscle in horses [35]. Safarzade et al. (2014) showed that resistance training enhances plasma levels of apoA-I in diabetic trained rats compared to a diabetic control group [36]. Garelnabi et al. (2014) aerobic exercise has no significant effect on liver apoA-I gene expression in C57BL6 LDLr −/− mice [37].

3.2. PON1

Romani et al. (2009) identified the endurance exercised rats have increased PON1 expression in plasma but exercise has no significant effect on liver microsomes PON1 expression [38]. Lee et al. (2012) showed that treadmill training enhances the plasma PON1 level in ovariectomized rat [39]. Nounou et al. (2012) found that swimming training showed a significant increase level of plasma PON1 in rats [40]. Garelnabi et al. (2014) showed that treadmill exercise training has no significant effect on liver PON1 gene expression in C57BL6 LDLr −/− mice [37].

3.3. ABCA1

Schweitzer et al. (2005) showed that aerobic exercise reduces heart ABCA1 expression [41]. Ghanbari-Niaki et al. (2007) showed that endurance exercise enhances ABCA1 gene expression in rat liver [42]. Khabazian et al. (2009) highlighted treadmill running exercise enhances intestine ABCA1 in rats [34]. Rocco et al. (2011) showed that treadmill-running exercise enhances liver ABCA1 expression in CETP-tg mice [43]. Zhang et al. (2011) found that swimming enhances liver ABCA1 expression in Otsuka Long Evans Tokushima Fatty rats [44]. Ghanbari-Niaki et al. (2013) highlighted that treadmill running exercise has no significant effects on heart ABCA1 gene expression in rats [45]. Kazeminasab et al. (2013) examined rats exercising on a motor-driven treadmill significantly increases liver ABCA1 gene expression in rats [46]. Meissner et al. (2013) showed that voluntary exercise has no significant effect on intestine ABCA1 gene expression in mice [47]. Ngo Sock et al. (2014) found that endurance exercise increases liver and intestine ABCA1 gene expression in ovariectomized + training rats than ovariectomized control rats [48]. Ngo Sock et al. (2014) found that endurance exercise enhances ileum ABCA1 expression in rats [49]. Garelnabi et al. (2014) highlights that treadmill exercise has no significant effect on liver ABCA1 gene expression in C57BL6 LDLr −/− mice [37]. Castro et al. (2017) showed that swimming exercise increased liver ABCA1 expression in both healthy and traumatic brain injury rats [50]. Ferreira et al. (2017) showed that Abca1 mRNA was not modified by endurance exercise in mice aorta [51]. Rahmati-Ahmadabad et al. (2018) showed that high intensity interval training enhances liver and intestine ABCA1 gene expression in rat [52]. Pinto et al. (2018) showed that aerobic exercise training did not change macrophages ABCA1 gene expression in 48 h after exercise program. However, exercise enhances macrophages ABCA1 gene expression observed immediately after a training program in mice [53]. Kazeminasab et al. (2018) showed that endurance training increased and ABCA1 transcripts in Wistar male rats [54].

Table 1
Details of the exercise training protocol and results for each study.

Author (year) [reference]	Mode of exercise	Days per week	Duration per session and intensity	Classification of intensity	No. of weeks	Animal	Results
Wei et al. 2005 [67]	Treadmill	7	30 min/day, 15 m/min	Low	2	C57 BL/6 mice	Increase in LDL receptor gene expression in the liver
Schweitzer et al. 2005 [41]	Running wheel	2	1 h periods of exercise in a large plastic box containing plastic tubes for exploration and movement	Low	60	Rat	Reduces heart ABCA1 expression
Ghanbari-Niaki et al. 2007 [42]	Treadmill	5	90 min/day, 0% grade, 25 m/min	Moderate	6	Rat	Enhances ABCA1 gene expression in liver
de Moraes et al. 2008 [33]	Treadmill	5	60 min/day, 0% grade, 18 m/min	Low	12	Rabbit	Increases apolipoprotein A-I expression in renal cortex
Wilund et al. 2008 [58]	Treadmill	5	Gradually increasing to 45 min of running by the end of the first week, 12–15 m/min, 65%VO_2 max	Moderate	12	C57L/J mice	Enhances duodenum ABCG5 and ABCG8, has no effect on jejunum and liver ABCG5 and ABCG8. Enhances liver SR-BI and LDL-r. enhances duodenum NPC1L1 and has no effect on jejunum NPC1L1
Khabazian et al. 2009 [34]	Treadmill	5	60 min/day, 0% grade, 25 m/min,	Moderate	12	Rats	Enhances plasma apoA-I and intestine ABCA1
Romani et al. 2009 [38]	Treadmill	3	1 h/day, 10% incline at increasing speed. The training protocol required a gradually increasing effort for 3 weeks to reach 65% VO_2 max, then continued for a further 7 weeks	Moderate	10	Rat	Increases PON1 expression in plasma and has no significant effect on liver microsomes PON1 expression
Richardson et al. 2009	Treadmill	4	30 min/day, 65–75% of maximal heart rate	Moderate	14	Pigs	Increases in apolipoprotein E in LDL compared to control and diabetic dyslipidemic groups
Bouwman et al. 2010 [35]	Training	4	Sessions of endurance training at 60% and 75% of HFest-max and high intensity training at 80% of HFest-max	Moderate and high	18	Horses	Enhances apoA-I expression vastus lateralis muscle
Meissner et al. 2010 [60]	Running wheel	7	Voluntary exercise	Low	2	Mice	Has no significant effect on intestine ABCG5 and ABCG8 gene expression.
Meissner et al. 2010 [59]	Running wheel	7	Voluntary exercise	Low	2	Old mice	Has no significant effect on liver ABCG5, ABCG8 and SR-BI.
Rocco et al. 2011 [43]	Treadmill	5	30 min/day, 15 m/min	Low	6	In CETP-tg mice	Enhances liver ABCA1 and LDL-r and reduces liver CYP7A1 expression. Has no significant effect on liver SR-BI expression
Zhang et al. 2011 [44]	Swimming	5	1 h/day	Moderate	12	Rats	Enhances liver ABCA1 expression
Ghanbari-Niaki et al.2012 [64]	Treadmill	5	60 min/day, 0% grade, 25 m/min	Moderate	8	Rats	Increases intestine ABCG8 gene expression and has no significant effect on kidney ABCG8 expression
Rahmati-Ahmadabad et al. 2012 [63]	Treadmill	5	60 min/day, 0% grade, 25 m/min	Moderate	8	Rat	Has no significant effect on liver ABCG8 expression
Lee et al. 2012 [39]	Treadmill	4	30 min/day	Low	12	Ovariectomized rat	Enhances the plasma PON level
Nounou et al. 2012 [40]	Swimming	5	one hour/day, 10 m/min	Moderate	6	Rats	Increases level of plasma PON 1
Zare Kookandeh et al. 2012 [55]	Treadmill	5	60 min/day, 0% grade, 25 m/min	Moderate	8	Rat	Increases ABCG1gene expression in small intestine
Ghanbari-Niaki et al. 2013 [56]	Treadmill	5	60 min/day, 0% grade, 25 m/min	Moderate	8	Rat	Enhances visceral fat ABCG1 and ABCG5 gene expression
Cote et al. 2013 [61]	Treadmill	5	Ran from 15 min/day at 15 m/min, 0% grade, up to 60 min/day at 26 m/min, 10% grade,75% of VO_2 max	Moderate	6	Rat	Has no significant effect on liver ABCG5 and CYP7A1 expression significantly increases intestine ABCG5, ABCG8 and CYP7A1 expression in rats, enhances liver ABCG8 expression.
Ghanbari-Niaki et al. 2013 [57]	Treadmill	5	60 min/day, 0% grade, 25 m/min	Moderate	8	Rat	Enhances ABCG4 gene expression in liver, small intestine, visceral fat not kidney tissues
Ghanbari-Niaki et al. 2013 [45]	Treadmill	5	60 min/day, 0% grade, 34 m/min	High	8	Rats	No significant effects on heart ABCA1 gene expression
Kazeminasab et al. 2013 [46]	Treadmill	5	60 min/day, 0% grade, 28 m/min	Moderate	8	Rats	Increases liver ABCA1 gene expression
Meissner et al. 2013 [47]	Running wheel	7	voluntary exercise	Low	12	Mice	Has no significant effect on intestine ABCA1 gene expression. Has no significant effect on liver and intestine ABCG5 and ABCG8 gene expression.

(*continued on next page*)

Table 1 (*continued*)

Author (year) [reference]	Mode of exercise	Days per week	Duration per session and intensity	Classification of intensity	No. of weeks	Animal	Results
Wen et al. 2013 [68]	Treadmill	5	26 m/min	Moderate	8	C57BL/6 mice	Hepatic LDLr expression was increases in or a high-fat + exercise group than high fat. There was no change in LDLR protein abundance in hepatic total tissue or membrane extracts between trained and untrained animals
Safarzade et al. 2014 [36]	Resistance training	3	6 repetitions/set		4	Rats	Enhances plasma levels of apoA-I in diabetic trained rats compared to a diabetic control group
Garelnabi et al. 2014 [37]	Treadmill	5	30 min/day, 15 m/min	Low	4	C57BL6 LDLr −/− mice	No significant effect on liver ABCA1 and PON1gene expression
Ngo Sock et al. 2014 [48]	Treadmill	5	From 15 min/day at 15 m/min, 0% grade for 2 weeks, up to 60 min/day at 26 etresm/ min, 10% grade, for the last 8 weeks	Moderate	10	Rats	Increases liver and intestine ABCA1 gene expression in ovariectomized + training rats than ovariectomized control rats. Increases SR-BI in training and ovariectomized + training than ovariectomized rats. Reduces LDLR in ovariectomized + training than ovariectomized rats
Ngo Sock et al. 2014 [49]	Treadmill	5	From 15 min/day at 15 m/min, 0% grade, for the first 2 weeks, up to 60 min/day at 26 m/min, 10% grade, for the last 4 weeks	Moderate	8	Rats	Enhances ileum ABCA1 and ABCG8 expression. Has no effect on ileum ABCG5 expression. Reduces ileum NPC1L1 expression
Pinto et al. 2015 [30]	Treadmill	5	30 min/day, 15 m/min	Low	6	C57BL/6N mice	Enhanced hepatic expression of SR-BI, LDLR and CYP7A1.
Ngo Sock et al. 2016 [69]	Running wheel	7	voluntary exercise	Low	3	Rats	Did not affect LDLR responses in Ovx rats. Liver LDLR gene expression was decreased in Ovx − training saline than Sham-Sed-Sal
Musman et al. 2016 [72]	Treadmill	5	30 min of coronary artery occlusion followed by 15 min of reperfusion (exercise without any exhaustion)	Low	4	Mice	Had no significant effect on liver CYP7A1 gene expression
Casquero et al. 2017 [66]	Swimming	5	60 min/day	Moderate	6	Mice	Had the independent effects on decreasing plasma CETP
Ferreira et al. 2017 [51]	Treadmill	5	60 min/day, 15 m/min	Low	6	Mice	Abca1 mRNA was not modified by exercise. Reduced the expression of Abcg1 in mice aorta
Castro et al. 2017 [50]	Swimming	5	60 min/day	Moderate	6	Rats	Increased liver ABCA1 expression in both healthy and traumatic brain injury rats
Farahnak et al. 2017 [70]	Rotating wheel	7	voluntary exercise	Low	5	Rat	Enhances liver LDLR expression in ovariectomized + high cholesterol diet and high cholesterol diet rat. Enhances liver CYP7A1 expression in variectomized and ovariectomized + high cholesterol diet rat.
Rahmati-Ahmadabad et al. 2018 [52]	Treadmill	5	30 min/day, 90%–95% of VO_2 max	High	10	Rat	Enhances liver and intestine ABCA1 gene expression. Enhances liver not intestine ABCG1 gene. Enhances intestine not liver SR-BI gene expression in rat
Pinto et al. 2018 [53]	Treadmill	5	30 min/day, 15 m/min	Low	6	Mice	Did not change macrophages ABCA1 gene expression in 48 h after exercise program. However, enhances macrophages ABCA1 gene expression observed immediately after exercise training program. Did not change macrophages ABCG1 gene expression. Did not change SR-BI in mice. Did not change CETP activity in mice.
Kazeminasab et al. 2018 [54]	Treadmill	5	60 min/day, 28 m/min	Moderate	8	Rats	Increased ABCA1 transcripts
de Bem et al. 2018 [62]	Treadmill	5	30 min/day, 0% grade, 50–60% maximal treadmill stress test	Low	4	Rat	Has no significant changes in liver ABCG5 and ABCG8
Rodrigues et al. 2018 [71]	Treadmill	5	1 h/day, 50–70% VO_2 max	Moderate	4	Mice	Alters hepatic morphology of low-density lipoprotein receptor knockout ovariectomized mice

3.4. ABCG1

Zare Kookandeh et al. (2012) highlighted that training increases ABCG1 gene expression in rat small intestine [55]. Ghanbari-Niaki et al. (2013) showed that endurance exercise significantly enhances visceral fat ABCG1 gene expression in rats [56]. Treadmill exercise reduced the expression of ABCG1 in mice aorta [51]. Rahmati-Ahmadabad et al. (2018) showed that high intensity interval training enhances liver not intestine ABCG1 gene expression in rat [52]. Pinto et al. (2018) showed that aerobic exercise training did not change macrophages ABCG1 gene expression [53].

3.5. ABCG4

The effects of exercise on ABCG4 has not been studied extensively. To the authors knowledge only one study has evaluated the effects of aerobic training on ABCG4. Ghanbari-Niaki et al. (2013) found treadmill exercise training enhances ABCG4 gene expression in liver, small intestine, visceral fat not kidney tissues [57].

3.6. ABCG5

Wilund et al. (2008) showed that treadmill exercise training enhances duodenum ABCG5 and has no effect on jejunum and liver ABCG5 in C57L/J mice [58]. Meissner et al. (2010) showed that voluntary training on running wheel has no significant effect on liver ABCG5 in old mice [59]. Meissner et al. (2010) also showed that training has no significant effect on intestine ABCG5 gene expression in mice [60]. Ghanbari-Niaki et al. (2013) showed that exercise training significantly enhances visceral fat ABCG5 gene expression in rats [56]. Cote et al. (2013) showed that continuous treadmill running exercise has no significant effect on liver ABCG5 expression significantly increases intestine ABCG5 expression in rats [61]. Meissner et al. (2013) showed that voluntary exercise has no significant effect on liver and intestine ABCG5 gene expression in mice [47]. Ngo Sock et al. (2014) showed that continuous treadmill exercise has no effect on ileum ABCG5 expression in rats [49]. de Bem et al. (2018) showed that exercise training has no significant changes in liver ABCG5 in rat [62].

3.7. ABCG8

Wilund et al. (2008) highlighted that treadmill running exercise enhances duodenum ABCG8 and has no effect on jejunum and liver ABCG8 in C57L/J mice [58]. Treadmill running exercise enhances duodenum ABCG8 and has no effect on jejunum and liver ABCG8 in C57L/J mice [58]. Meissner et al. (2010) showed that voluntary training has no significant effect on intestine ABCG8 gene expression in mice [60]. Meissner et al. (2010) showed that voluntary training has no significant effect on liver ABCG8 in mice [59]. Rahmati-Ahmadabad et al. (2012) showed that aerobic training has no significant effect on liver ABCG8 expression in rats [63]. Ghanbari-Niaki et al. (2012) showed that exercise increases intestine ABCG8 gene expression and has no significant effect on kidney ABCG8 expression in rats [64]. Cote et al. (2013) showed that continuous running on a rodent treadmill enhances liver and intestine ABCG8 expression in rats [61]. Meissner et al. (2013) found that voluntary running has no significant effect on liver and intestine ABCG8 gene expression in mice [47]. Ngo Sock et al. (2014) showed that exercise training enhances ileum ABCG8 expression in rats [49]. de Bem et al. (2018) highlighted exercise training on treadmill has no significant changes liver ABCG8 in rat [62].

3.8. ApoE

The effects of exercise on apoE is not studied extensively in animals. Richardson et al. (2009) found that endurance exercise induced increases in apolipoprotein E in LDL compared to control and diabetic dyslipidemic groups in pigs [65].

3.9. SR-BI

Wilund et al. (2008) showed that exercise enhances liver SR-BI in C57L/J mice [58]. Meissner et al. (2010) showed that voluntary training has no significant effect on liver SR-BI in mice [59]. Rocco et al. (2011) showed that treadmill exercise training has no significant effect on liver SR-BI expression in CETP-tg mice [43]. Ngo Sock et al. (2014) showed that endurance training increases SR-BI in training and ovariectomized + training than ovariectomized rats [48]. Pinto et al. (2015) showed that aerobic exercise training enhanced hepatic expression of SR-BI in C57BL/6N mice [30]. Rahmati-Ahmadabad et al. (2018) showed that high intensity interval training enhances intestine not liver SR-BI gene expression in rat [52]. Pinto et al. (2018) showed that aerobic exercise training did not change SR-BI in mice [53].

3.10. CETP

The effects of training on CETP are not studied extensively in animals. Casquero et al. (2017) found that swimming training had the independent effects on decreasing plasma CETP in mice [66]. Pinto et al. (2018) showed that aerobic exercise training did not change CETP activity in mice [53].

3.11. LDLr

Wei et al. (2005) highlighted aerobic exercise showed an increase in LDL receptor gene expression in the liver of C57 BL/6 mice [67]. Wilund et al. (2008) found endurance exercise enhances liver LDL-r in C57L/J mice [58]. Rocco et al. (2011) showed that treadmill exercise increases liver LDL-r expression in CETP-tg mice [43]. Wen et al. (2013) showed that hepatic LDLr expression in C57BL/6 mice was increases in or a high-fat + exercise group than high-fat. There was no change in LDLR protein abundance in hepatic total tissue or membrane extracts between trained and untrained animals [68]. Ngo Sock et al. (2014) showed that exercise on treadmill reduces LDLR in ovariectomized + training than ovariectomized rats [48]. Pinto et al. (2015) showed that aerobic exercise training enhanced hepatic expression of LDLR in C57BL/6N mice [30]. Ngo Sock et al. (2016) showed that exercise training did not affect LDLR responses in Ovx rats. Liver LDLr gene expression was decreased in Ovx − training saline than Sham-Sed-Sal [69]. Farahnak et al. (2017) showed that voluntary exercise enhances liver LDLr expression in ovariectomized + high cholesterol diet and high cholesterol diet rat [70]. Rodrigues et al. (2018) showed that exercise training on ergometric treadmill alters hepatic morphology of low-density lipoprotein receptor knockout ovariectomized mice [71].

3.12. CYP7A1

Rocco et al. (2011) found that aerobic exercise decreases liver CYP7A1 expression in CETP-tg mice [43]. Cote et al. (2013) showed that continuous running on a treadmill has no significant effect on liver CYP7A1 expression and increases intestine CYP7A1 expression in rats [61]. Pinto et al. (2015) showed that aerobic exercise training enhanced hepatic expression of CYP7A1 in C57BL/6N mice [30]. Musman et al. (2016) showed that exercised mice without any exhaustion had no significant effect on liver CYP7A1 gene expression [72]. Farahnak et al. (2017) showed that voluntary exercise enhances liver CYP7A1 expression in variectomized and ovariectomized + high cholesterol diet rat [70].

3.13. NPC1L1

Wilund et al. (2008) showed that treadmill-running exercise enhances duodenum NPC1L1 and has no effect on jejunum NPC1L1 in

C57L/J mice [58]. Ngo Sock et al. (2014) showed that continuous running on treadmill reduces ileum NPC1L1 expression in rats [49].

4. Discussion

The findings of the studies highlighted in this review show that exercise training (lower than 4 weeks) has no significant effects on RCTr [59,60]. However, one study showed that 5 weeks of voluntary exercise enhances liver LDLr expression in ovariectomized + high cholesterol diet and high cholesterol diet rats, as well as, enhances liver CYP7A1 expression in variectomized and ovariectomized + high cholesterol diet rat [70], so > 4 weeks could be essential for these markers in particular.

Exercise training up to 12 weeks of voluntary exercise has no significant effect on intestine ABCA1 gene expression, as well as, has no significant effect on liver and intestine ABCG5 and ABCG8 gene expression [47]. Longer duration training protocols appear to have more significant effects than shorter protocols in that 60 weeks of voluntary exercise reduces heart ABCA1 expression [41].

It is evident that most studies use treadmill jogging or running as the mode of exercise and the rat is the most frequently used animal. This is because they have a similar genome to humans. In addition, their control and maintenance is convenient for researchers.Intensity is most commonly reported as meters/min in which the authors have categorised as low intensity ($\leq$18 m/min), moderate intensity (19–28 m/min) and high intensity (more than $\geq$29 m/min). The findings reagrding low-intensity exercise are mixed, with some studies showing no significant effects on RCTr [37,53]. However, some showed significant effects on RCTr elements in responses to low-intensity exercise [43,58,67]. It is notable that, the effective low-intensity exercise reported in animal studies that use mice [43,58,67] is different to studies that used rats [37,53]. It possible the type of animals is important and will influence the findings.

Research is clear that moderate-intensity exercise significantly changes RCTr elements. The majority of the research has investigated the effects of moderate-intensity exercise exercise on RCTr elements. However, they used fixed intensity of aerobic exercise and other exercise modes and types has not been investigated substantially. Research examining high-intensity exercise is minimal as has only been examined in two studies [45,52] (Table1). Overall, it seems that higher than lower- intensity training enhances liver and intestine ABCA1 gene expression, as well as, enhances liver but not intestine ABCG1 gene expression and enhances intestine not liver SR-BI gene expression in rat [52]. Future research should be undertaken to determine the different effects of type and intensity of exercise on RCTr elements.

The mechanisms related to effects of exercise on RCTr is still unclear. However, there were several posited mechanisms to identify the positive effects of exercise on lipid profile to consequently decrease the risk of cardiovascular disease development (Fig. 3). Nuclear receptors are a large family of the abundant transcriptional genes whose role is to regulate wide gene expression in the animal kingdom. They are recognized as nuclear hormone receptors which act as ligand-activated transcription factors. Studies have shown these receptors participate directly in connection to several signaling molecules in control of transcription responses and processing. As suggested and classified by Robinson-Rechavi et al. (2003), nuclear receptors with natural ligand which bind to small molecules and non-natural ligand or nuclear orphan receptors [73]. However, Chawala et al. (2001) identified there might be numerous nuclear receptors; endocrine receptors (lignds; high-affinity hormonal lipids),adopted orphan receptors (ligand; low-affinity dietary lipids), and orphan receptors (ligands; unknown) [74].

When considering the role of these receptors involved in HDL biogenesis elements and also in cholesterol efflux via activation, the most and very common nuclear recptors could be focused on adopted orphan receptors lignad to dietary lipids at low-affinity such as; retinoid X receptors (RXR α, β, and γ, the common heterodimer partners) peroxisome proliferator-activated receptors (PPAR α, γ, and δ the fatty acids sensors), liver X receptors (LXR α, β, the sterol sensors), farnesoid X receptor (FXR, the bile acids sensor), and the constitutive androstane receptor (CAR) and pregnane X receptors (RXR) and steroid xenobiotic receptors (SXR) which are recognized as xenobiotic sensors. It has been shown that some of the adopted orphan nuclear receptors play more effective and crucial role in cholesterol efflux via stimulating RCT process through the ATP- binding cassette transporters, particularly ABCA and ABCG family members [75,76]. In this regard, LXR seems to be in the center of the cholesterol efflux from tissues toward liver.

Repa et al. (2000), showed that several nuclear receptors that formed heterodimers with the RXR complex, such as PPAR, regulate ABCA1 gene expression. [77]. Oliver et al. (2001) found that macrophages, lymphocytes, and intestinal cells increased ABCA1 gene expression and induced an increase in ApoA-1 cholesterol uptake, when cells were treated with PPAR agonist [78]. They showed that PPAR agonist treatement has positive effect on HDL and LDL regulation [78]. PPARs have receptors like LXR that regulate the expression of genes controlling fat. Butcher et al. (2008) showed that eight weeks endurance training increased LXR gene expression. They have suggested that the activation of the PPAR ligand leads to the initial activation of LXR and eventually LXR causes upregulation of ABCA1 and ABCG1 [79].

Rahmati-Ahmadabad et al. (2018) showed that high-intensity interval training induced an increase in liver LXR gene expression that has positive correlation with liver ABCA1 gene expression [80]. They found that FXR suppresses CYP7A1 in the intestine [81]. PXR promotes CYP7A1 expression in mice [82,83]. However, one study did not comfirm the effects of PPAR on regulation of lipid and glycemic metabolism in RCTr. Greene et al. (2012) showed that exercise-induced activation of PPAR isoforms [84]. They showed that training increased 39% protein content of PPAR alpha and 122% protein content of PPAR alpha in muscle. In addition, training induced an increase in AMPK content, FAT/CD36, lipoprotein lipase, CPT-1 and COX-IV. However, the protein content of ABCA1 and LDLR did not differ in control and trained groups.

Increase in AMPK content ispositively correlated with HDL concentration. In addition, increase in PPAR delta has a negative correlation with LDL concentrations. However, the protein content of ABCA1 and LDLR did not difference in control and trained groups. Generally, physical training increases the expression of AMPK and PGC1-alpha to activation of PPAR. In adition, physical training increases the expression of LXR. Consequntly, PPAR, LXR, FXR and PXR induced changes in some genes related to oxidative metabolism and transport of lipoproteins.

Several studies highlight that thyroid hormones and thyromimetics have regulatory effects on RCTr elements. Plasma apoAI levels enhances responces to triiodothyronine (T_3) and the thyromimetic (CGS-23425) hormones [85,86]. In addition, thyroid hormones and thyromimetics to stimulate SRBI, CYP7A1, ABCG5 and ABCG8 [87–90]. It is reported that thyroid hormone receptor beta mediated the effect of T3 on the stimulation of CYP7A1 expression [87]. Eight weeks treatment with thyromimetic T-0681, up-regulation of both hepatic ABCG5/G8 and CYP7A1 in apoE knockout mice [89]. Pedrelli et al. (2010) suggest that thyroid hormone receptor beta stimulate RCT and decrease atherosclerosis in animal models [91]. Sex hormones also effects lipid metabolism [92].

Insulin signal transduction alters lipid and lipoprotein metabolism [93]. Several studies showed that pro-inflammatory factors such as interferon-gamma (IFN-γ), endotoxin, tumour necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1β), regulate cholesterol efflux via changes in RCTr process. The incubation of foam cells with IFN-γ results in the reduction of HDL3-mediated cholesterol efflux [94]. This decrease is not observed in other macrophage-activating factors, such as colony-stimulating factor. These findings suggest that IFN-γ contributes to the progression of an atherosclerotic lesion by altering the pathway of intracellular cholesterol trafficking in macrophage foam cells.

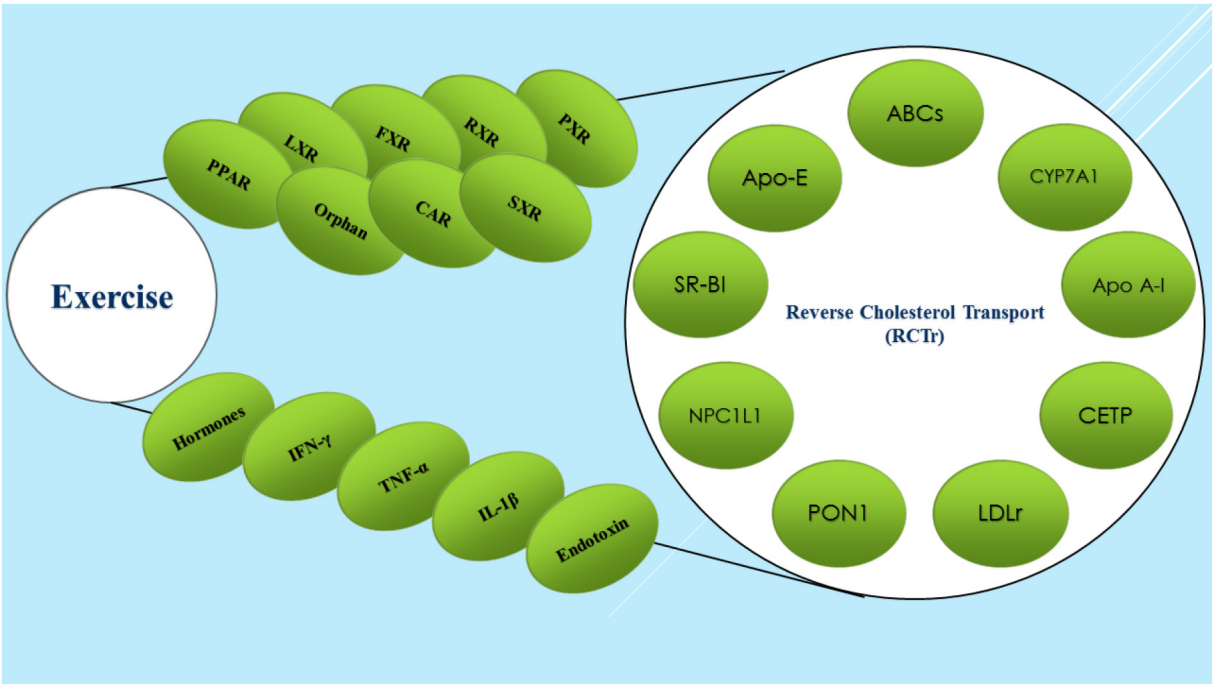

Fig. 3. The mechanisms related to effects of exercise on RCTr.

Khovidhunkit et al. (2003) showed that the mRNA levels of ABCA1 and ABCG1 are decreased in responce to endotoxin or cytokines such as TNF-α and IL-1β [95]. Transforming growth factor beta (TGF-β) enhances the cholesterol efflux mediated by apoA-I or HDL that consistent with an increase in ABCA1 expression [96].

5. Conclusion

Exercise has a positive impact on atherosclerosis and reducing the risk of CVD, a major concern of today's health care systems. It is important to emphasize that the positive effects of physical training on CVD are thought to be mediated by diverse mechanisms, including the alteration of elements of the RCTr process. The aim of this article was to review the effects of any types of exercise training (more than two weeks) on RCTr elements in animal models. After evaluating available literature in animals from PubMed, Science direct and Google Scholar, it is clear that most of the studies investigate the effects of aerobic training on RCTr elements and effects of other types of training are poorly understood. The findings of this review suggests that moderate to higher intensity and longer-term protocols have more significant effects than lower intensity activity and short-term protocols on RCTr in animal models. PPAR, LXR, FXR and PXR and several hormones and cytokines affect RCTr elements though mechanisms of exercise induced RCTr changes are unclear. Future research should determine these mechanisms as well as examine various modes and high intensity exercise.

Conflicts of interest

The authors have no conflicts of interest to declare.

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None.

Contributions

SRA conceived and designed this study. SRA collected the studies. SRA and DRB wrote the manuscript. HSH rechecked the collected studies. AGN revised and improved the quality of the paper. All authors read and approved the final version of the manuscript.

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