REVIEW

Interactions Between Statins, Exercise, and Health: A Clinical Update

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CARDIOVASCULAR DISEASE

Cardiovascular disease (CVD) is a major source of morbidity and mortality across the globe (1). The Global Burden of Disease study, which includes epidemiological estimates of disease from 204 countries between 1990 and 2019, established that CVD is the leading cause of death worldwide (2). CVD is also a major source of reduced quality of life due to related illnesses. In 2019, there were 523 million cases of CVD, 18.6 million deaths, 34.4 million living with a CVD-related disability, and nearly 400 million years of life lost or disability-adjusted life years due to CVD (2). Considering the large impact CVD has on disability-adjusted life years, improving *healthspan*, defined as the period someone spends healthy and free from chronic disease (3,4), is becoming critically important as modern medical capability improves lifespan expectancy. *J Clin Exerc Physiol*. 2022;11(2):54–61.

EXERCISE

Regular exercise is a commonly prescribed therapeutic intervention for the mitigation of CVD and improvements to healthspan (5–8), which is particularly important in older individuals (9). However, we and others have also advocated that daily exercise (or moderate to vigorous physical activity) is obligatory for normal health and wellness and not just an intervention that improves health (10). A common measurement used to assess overall health and fitness is cardiorespiratory fitness (CRF), which can be increased or maintained during the aging process with regular moderate to vigorous exercise (11,12). Recent reviewers have summarized evidence indicating that improvements in CRF play an integral role in reducing not only CVD but also incident myocardial infarction, hypertension, diabetes, atrial fibrillation, heart failure, stroke, and all-cause mortality (13,14). Moreover, the American Heart Association published a position paper stating that CRF should be a vital sign for clinical care (15). Hence, exercise has been explored and used as an intervention that can both prevent and, in some cases, treat various chronic metabolic diseases. Despite strong evidence that physical activity reduces the risk of preventable chronic disease conditions, including CVD, authors of a 2008 study reported the number of people who met recommended governmental activity guidelines in the US as extraordinarily low, including >90% of US adults not meeting goals of 150 min·week^{-1} of moderate to vigorous activity (16). Authors of a more recent study from 2018, however, reported the number of US adults between the ages of 18 and 64 who did not meet the recommended physical activity guidelines decreased (77.1%) between 2010 and 2015, yet those meeting the recommended guidelines remain low (17). Additionally, the World Health Organization reported in 2018 that 80% of adolescents do not meet recommended physical activity criteria across the globe (18). Since exercise goals are not being met, clinicians have increasingly turned to pharmacotherapy to prevent and/or treat chronic diseases. As exercise is a common intervention prescribed to improve healthspan, there is a critical need to understand the interactions of exercise when used in combination with medications prescribed for chronic disease prevention such as CVD.

STATINS

Statins are a common prescription as a secondary prevention method to reduce the risk for CVD events/revascularization interventions (19–21). Statins are cholesterol-lowering

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drugs that do so via inhibition of 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMG-CoA reductase), a rate-limiting enzyme for hepatic cholesterol synthesis (22,23). There are 2 forms of statins, lipophilic and hydrophilic, due to polar or nonpolar substituents. The lipophilic statins (simvastatin, atorvastatin, etc.) move passively through the cell membrane resulting in extrahepatic tissue uptake in addition to the liver, whereas hydrophilic statins (pravastatin) require carrier-mediated uptake and primarily target the liver (22). Statin therapy is a highly effective secondary prevention method that reduces CVD-related mortality, all-cause mortality, coronary events, ischemic strokes, and postmyocardial infarction recovery (20,21,24,25). While statins generally achieve similar effects, some contend that high-intensity statins (i.e., rosuvastatin (20 or 40 mg) and/or atorvastatin (40 or 80 mg)) are preferred in secondary prevention and yield significantly lower subsequent mortality rates than other statins (26). In the past, statins were primarily prescribed after a CVD event, for those with type 2 diabetes, or for those with familial hypercholesteremia (FH). However, guidelines were established by the American Heart Association/American College of Cardiology in 2013 that sought to dramatically increase statin use for primary prevention (27). A recent 20-year follow up of children taking statins for FH revealed a reduced risk for CVD in adulthood (28). Because of these guidelines and strong evidence for reducing CVD events, statins have become some of the most widely prescribed drugs in the world. Over 43 million Americans are taking a statin, and atorvastatin was the second most prescribed medication in the world (104,000,000) in 2019 (3,29). As statin therapy use becomes more common, its benefits and risks must be better understood so informed decisions can be made. This is particularly important when considering statins as primary prevention care in disease-free individuals at increasingly younger ages (30), including usage in children with extreme obesity or FH (31).

While statins and regular exercise are independently effective treatments for reducing CVD risk, authors of one large study in a cohort of VA patients suggest that combined treatment significantly reduces CVD risk to an even greater degree than either exercise or statin therapy alone (32). However, statin therapy is not without risk for potential adverse side effects, including statin-associated muscle symptoms (SAMSs), gastro-intestinal discomfort, fatigue, liver enzyme elevation, mitochondrial abnormalities, peripheral neuropathy, insomnia, neurocognitive symptoms, and a modest but significant and consistent increase in the risk of type 2 diabetes (33–35). Moreover, authors of a recent study found that type 2 diabetes patients who take statins have worsening markers of glycemic control and require higher doses of glucose lowering medications (36). Statin-induced symptomology is primarily associated with the musculoskeletal system such as pain (i.e., myalgia), which is a critical tissue involved in physical activity (37–39). Therefore, it is important to understand the potential interaction between statins and exercise, as it could affect ambulation, physical activity, muscle function, and maintenance or improvement of CRF in individuals throughout the lifespan (40).

Impact on Exercise and Physical Activity Behavior

Due to the enhanced impact of combined exercise and statin therapy on CVD risk, physicians regularly coprescribe these 2 treatments together. However, the most common adverse side effect SAMSs impacts both adherence to statin therapy and raises concerns of reduced physical activity levels while taking statins (41). Clinical data indicate that up to 30% of patients have complaints of SAMSs (42,43). Muscle damage is typically substantiated by elevated levels of serum creatine kinase (CK) concentrations. Authors of some reports even suggest statins may exacerbate exercise-induced muscle damage, evidenced by elevated CK levels postexercise (44). Most cases of statin-induced muscle pain, however, are associated with normal or slightly elevated CK concentrations, indicating minimal to no muscle damage. While authors of many studies do not suggest statin therapy induces muscle damage, 65% of former statin users state the main reason for nonadherence or discontinuation was the onset of muscle-related side effects (45). When patients are blinded to treatment in randomized controlled trials, minimal differences are observed in the prevalence of SAMSs between statin and placebo users (46,47). Despite this, in many cases in which individuals have SAMSs, the cessation of such symptoms is often only achieved through the discontinuation of statin therapy (45,48). Apprehension that physical activity may induce and/or exacerbate SAMSs may further impact physical activity levels or exercise habits (49). The literature on statin-specific impact to physical activity levels is mixed. For example, authors of a prospective cohort study of 5,994 men over the age of 65 years demonstrated that statin users had a greater decline in self-reported physical activity (50). Authors of similar observational studies have demonstrated statin prescription is widely associated with reduced physical activity levels. These authors indicate statin users partake in less moderate and vigorous physical activity than nonusers, had increased sedentary behavior, and had reduced odds of resistance exercise activities (51,52). The Effects of Statins on Skeletal Muscle Function and Performance (STOMP) study, a randomized, double-blinded clinical trial, also demonstrated greater sedentary time in the oldest age group (>55 years) of patients who were prescribed 80 mg of atorvastatin and followed for 6 months (53). However, the youngest age group showed greater physical activity, and overall, the STOMP study found no differences in physical activity levels between participants undergoing statin therapy compared with placebo (53). Conversely, authors of 2 studies have demonstrated patients with leg claudication who received statin therapy (atorvastatin or simvastatin) had increased exercise tolerance exhibited by increased pain-free walk time and distance on a treadmill compared with placebo-treated subjects, which the authors suggest may be due to plaque stabilization and a potential improvement in endothelial function (54,55). These findings suggest statin therapy may improve

exercise capacity in some patient populations, perhaps those with advanced disease. While statins may impact the incidence of exercise-related muscle complaints, inconsistent findings suggest that SAMSs do not regularly result in reduced physical activity (40). These variable responses could be due to various factors such as whether patients were already habituated to high daily physical activity patterns or regular exercise, had elevated CRF before statin therapy, the dosage of statin therapy (dose ranges from 10 to 80 mg·day^{-1}), or the type of statin (lipophilic versus hydrophilic) among other factors including genetic polymorphisms that control the capacity to catabolize the drug and thus impact muscle exposure to statins (56).

Muscle Function

Extensive work has identified the epidemiological impact of SAMSd, whereas more recent work has focused more closely on the extent by which these symptoms are accompanied by functional declines in muscle function and/or CRF. While the percentage of individuals who exhibit markers of skeletal muscle myopathy (e.g., serum CK) is low (57), statins may impair critical skeletal muscle function such as strength. Muscular strength is also a critical component of healthspan, as reduced strength is associated with greater risk of falls in older adults, and falls in older adults increase risk of mortality (58–61). Evidence for reduced muscle strength with statin therapy was first noted in a series of case reports in which 4 symptomatic statin users exhibited weakness upon strength testing that was reversed when statin treatment was stopped (62). Authors of a more recent small study showed similar findings in which an intrinsic muscle defect was identified in asymptomatic and symptomatic statin users using electrical quadricep stimulation, further suggesting a potential deficiency in muscle function (63). Authors of larger studies, however, have not provided evidence to support an intrinsic loss of muscle strength with statin therapy. Limited data suggest that statins directly impair resistance and/or exercise capacity independent of changes to physical activity. The authors of the STOMP study did, however, demonstrate that statin users with musculoskeletal complaints exhibited lower muscle strength in 4 of 15 strength tests, independent of any changes in physical activity levels (53). Additionally, statin users in the STOMP study also had a greater frequency of myalgias, particularly in older adults, and an increase in CK compared with placebo, suggesting greater muscle damage (53). Authors of a summary of 3 investigations assessing muscle strength in participants after short-term statin therapy treatment showed no significant decrements in muscle strength even in participants with statin-induced myalgia (64). However, short-term statin therapy is not common in clinical practice, which may contribute to various findings in muscle strength and function (65). Some authors have found that resistance training combined with statin therapy yielded positive results (e.g., improved muscular strength), like individuals who performed resistance training alone (66,67). Collectively, while authors of initial studies provided evidence that statins may impede muscle function, authors of large scale and more recent studies suggest no interaction exists whereby statin therapy impedes the beneficial effects of resistance exercise.

CRF

As discussed above, CRF is a functional measure that is inversely associated with CVD, numerous other disease states (e.g., cancer, type 2 diabetes, nonalcoholic fatty liver disease), and all-cause mortality that can be readily modified by regular exercise (68). Statin therapy is also an effective intervention yielding similar reductions in CVD risk (26). Considering this, our lab previously conducted a study in which our hypothesis was that statin therapy (simvastatin 40 mg·d^{-1}) plus a 12-week exercise intervention (5 d·week^{-1} at 45 min·d^{-1} of monitored exercise on treadmills) compared with an exercise intervention alone would have a synergistic effect on lowering metabolic syndrome risk factors in physically inactive participants with 2 of the 5 metabolic syndrome risk factors (National Heart Lung and Blood Institute) (69). In contrast to our hypothesis, we found participants receiving statin therapy plus exercise did not increase absolute or relative measures of CRF when compared with those who performed exercise training without statin therapy. The exercise-alone group had a 13% increase in peak VO_2, while no increase occurred in the statin plus exercise group, an effect that was uniform among all participants (n = 19). After further investigation, we identified that individuals who underwent exercise and statin therapy did not exhibit typical exercise-induced increases in measures of skeletal muscle mitochondrial content when compared with the exercise-alone group, agreeing with the CRF findings. Collectively, our findings suggest that statin therapy initiated at the same time as an exercise intervention blocks normal exercise-induced improvements in CRF and skeletal muscle mitochondrial density in individuals who were previously sedentary and have metabolic syndrome risk factors. These findings are important, as CRF is a critical factor for improving/maintaining healthspan later in life. However, authors of cross-sectional studies have demonstrated that older individuals can be both long-term statin users and highly fit (32). Authors of a more recent study which recruited participants with dyslipidemia and other comorbidities for statin intervention, statin plus exercise, or exercise intervention alone demonstrated that both exercise and combined statin therapy with exercise resulted in similar increases CRF and functional status, whereas statin treatment alone caused a moderate reduction in these measures (70). Similarly, statin therapy did not attenuate the exercise training response in heart failure patients or those undergoing cardiac rehabilitation (71,72). Authors of studies in other populations with chronic disease exhibited the beneficial effect of exercise training on CRF, even when undergoing statin therapy. It is unknown why, in our study, we found that statins blunted exercise adaptations, but our results are the only ones that used the same dose and type of statin in such a study; moreover, our study was unique in that we initiated exercise and statin therapy at the same time. The participants were sedentary and had low baseline CRF along with metabolic

syndrome risk factors. These attributes are linked to lower mitochondrial content and function in skeletal muscle which may increase susceptibility for statins to interfere with exercise adaptations. Much remains to be uncovered regarding the potential interactions between statin therapy and exercise training specific to certain clinical populations.

Future Directions

Some less investigated questions remain regarding the possible effects of statins on muscle health, CRF, metabolic risk (type 2 diabetes), and optimal methods for combining the beneficial effects of statin therapy with the beneficial effects of exercise interventions or increased moderate to vigorous physical activity in daily life. A primary question in the field is the importance of dose and duration of statins on potential adverse outcomes (65). Although different doses of different types of statins have been tested to quantify their cholesterol-lowering benefits, much less is known about dose effects on primary and secondary prevention, adherence, and long-term toxicity. Standard doses for atorvastatin, for example, can range from 10 to 80 mg a day (30). In a meta-analysis of over 10,000 patients, the highest dosing received the greatest secondary prevention benefits in terms of reduced ischemic stroke and cardiovascular events (24). In a review of evidence for primary prevention by the US Preventive Services tasked to provide recommendations, statin therapy decreased risk for all-cause mortality, CV mortality, stroke, myocardial infarction, and composite cardiovascular outcomes (30). Authors of the review also found no increased risk for myalgia, serious adverse events, or liver damage. They also found that increased reduction of low density lipoprotein was associated with decreased CVD event risk, with greater benefits to those at higher risk (30). Unfortunately, authors of this study did not address long-term dosage effects. Authors of a similar study noted reduced incidences of markers of CVD in a FH cohort after 20 years of statin therapy, but no examinations of CRF or physical activity were made (28).

Our research group is performing an ongoing National Institutes of Health trial to address the dose and duration effects of statin therapy on a variety of outcomes (NIH R01AR071263). The design and outcome measures are summarized in Figure 1. The goal of our clinical and translational study is to provide insight into some of the challenges and missing information discussed in this review. In our study, we assess the effects of statins in disease-free individuals, primarily defined as those with no diagnosed metabolic disorders, between the ages of 35 to 65 for whom physicians might consider using a statin as a primary prevention method. The aim of our randomized controlled, double-blinded clinical trial is to understand the impact of low (20 mg atorvastatin) versus high dose (80 mg atorvastatin) statin therapy versus placebo on primary outcome measures of skeletal muscle mitochondrial respiratory function, insulin sensitivity, and CRF. Additional secondary outcome measures include muscle strength, functional assessments (sit to stand test), muscle pain, submaximal exercise substrate utilization rates, physical activity and sedentary behavior measured by accelerometers, CK levels after maximal exercise, and noninvasive measures of muscle mitochondrial function measured by near-infrared spectroscopy. The study has 2 distinct aims. The first aim is to examine dose × duration (baseline, 1, 6, and 12 months) effects with no intervention on activity levels or exercise behavior, whereas the second aim is focused on investigating exercise and statin interactions. The same participant population in the second aim are undergoing a monitored 12-week exercise intervention (5 $d \cdot week^{-1}$, 45 $min \cdot d^{-1}$, 60%–75% peak VO_2) while also being prescribed the same statin or placebo regiment as aim 1. Outcome measures in aim 2 will be assessed at baseline and 1- and 3-month timepoints.

A primary goal of our study is to determine if a lower dose of statin causes long-term adverse effects on CRF and insulin sensitivity and allows for normal beneficial exercise adaptations regarding improvements in CRF and insulin sensitivity. Both aims will provide critical information to clinicians who are treating patients that could benefit from statin therapy for primary prevention in addition to exercise/physical activity interventions.

HEALTHSPAN/FUTURE

Clinicians not only want to prevent cardiac events and increase lifespan but also have an increasing concern about healthspan. Whether the primary use of statins as a tool for primary prevention prolongs or shortens healthspan is an important question. As such, the field does not yet understand how the combination of therapies (i.e., statin therapy, exercise training, combined statin and exercise) impact primary prevention or treatment. Thus, further investigations need to be conducted to understand the impact of statins on the ability to perform regular exercise and respond positively to exercise training or rehabilitation. Basic science studies focused on identifying the mechanisms of action, both beneficial and toxic, of statins within the physiological system are also needed to inform the use of statins moving forward. Concerns are reported in the literature regarding negative outcomes after statin therapy in the brain and nervous system, hepatic system, muscles, cardiovascular system, insulin-sensitivity, and CRF (22). We also do not know if adverse effects of statin therapy have greater prevalence when an individual takes a statin for a long period of time. Understanding these long-term risks is paramount, as approximately 10% of children qualify for statin therapy, and that number continues to rise (73,74), with evidence suggesting this puts them at an increased risk for type 2 diabetes (75). Finally, it remains unknown whether there is a difference in the risk/benefit profiles of different populations, especially underrepresented minority and socioeconomically disadvantaged groups, individuals that have a family history of metabolic disorders, or those with comorbidities.

CONCLUSION

In summary, statins may increase the incidence of musculoskeletal complaints, augment exercise-induced damage, and negatively impact CRF, but data on these outcomes remain

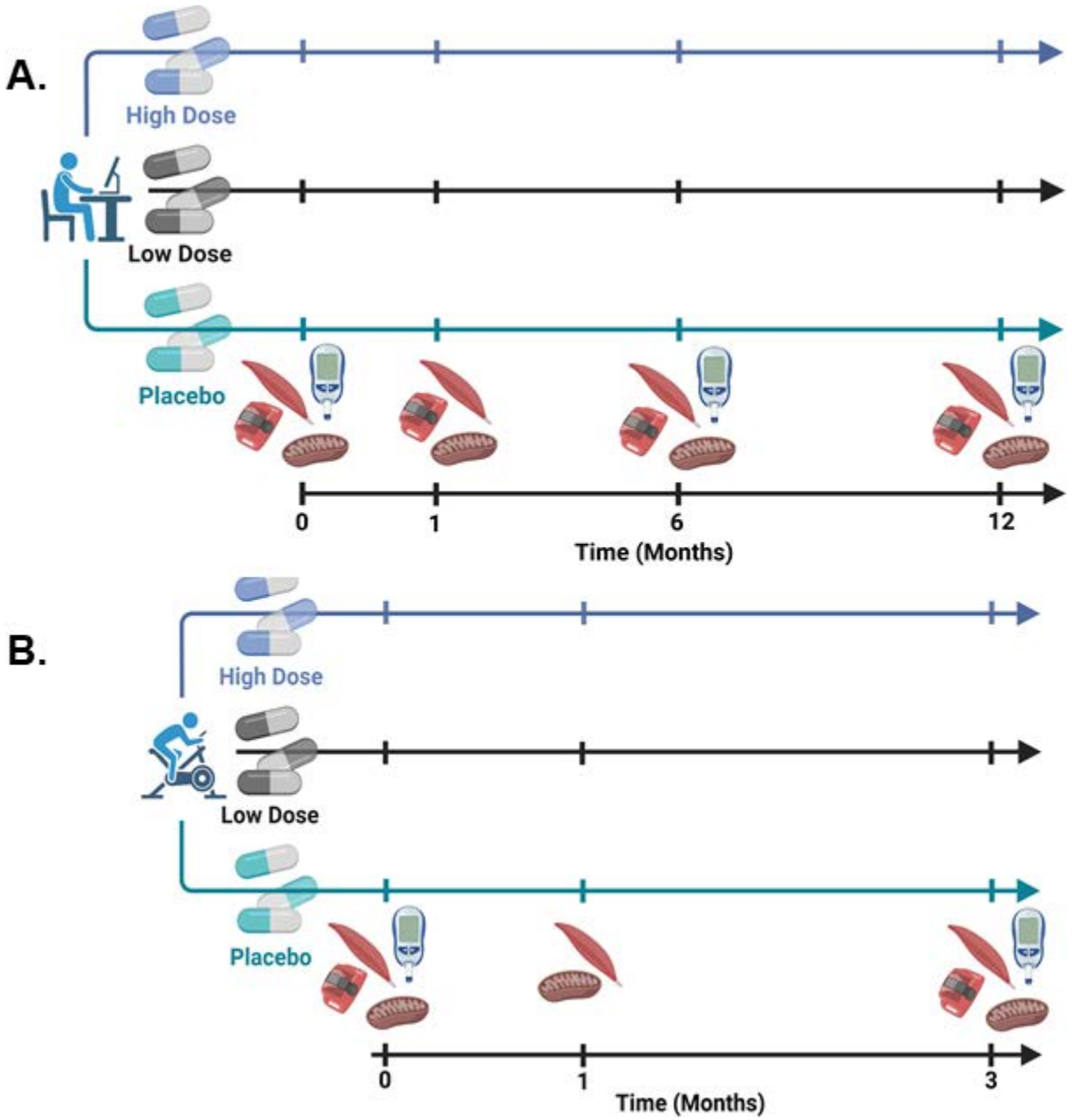

FIGURE 1. NIH R01AR071263 Study design and outcome measures. This randomized controlled, double-blinded clinical trial is designed to assess the impact of placebo, low (20 mg), or high (80 mg) dose statin therapy (Atorvastatin) in disease-free individuals, defined as those with no diagnosed metabolic disorders, yet may be considered for statin therapy as a primary prevention method by physicians. Primary outcome measures include skeletal muscle mitochondrial respiratory function, insulin sensitivity, and cardiorespiratory fitness. Secondary outcome measures include muscle strength, functional assessments, muscle pain, submaximal exercise substrate utilization, physical activity, and sedentary behavior. (A) Aim 1 of this study is to examine the impact of dose and duration on primary and secondary outcome measures with no intervention on activity levels or exercise behavior over a 12-month period. (B) Aim 2 is to investigate the interaction of exercise training and statin therapy on primary and secondary outcome measures. Participants from the same study population are undergoing a 12-week (3-month) exercise intervention (5 $d \cdot week^{-1}$, 45 $min \cdot d^{-1}$, monitored exercise) while also undergoing the same statin or placebo therapy as Aim 1.

mixed, and more definitive studies are needed. An objective review of available data indicates that statin therapy does not consistently reduce physical activity, muscle function, or overall exercise performance (i.e., CRF). These inconsistent findings may be due to various experimental differences (described above) and the lack of true randomized control studies focused on these questions. As with many pharmacological agents, we know very little about how statins interact with exercise over a prolonged period to impact health and CVD risk. This is particularly important when considering the heightened call for statin therapy combined with exercise or physical activity interventions for prevention of CVD.

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