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Review

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ABSTRACT

Abdominal aortic aneurysm (AAA) is a prevalent condition which causes progressive growth and rupture of aortic wall with a high death rate. Several studies have found that treatment with statins may decrease the progress of AAA and the risk of rupture by suppressing the inflammatory mediators, decreasing oxidative stress, and inhibiting mechanisms involved in extracellular matrix (ECM) degradation. Moreover, some studies have reported that prehospital therapy with statins can decrease mortality after surgery. The novelty of this paper is that different studies including those performed in humans and animals were reviewed and the potential mechanisms by which statins can have an effect on AAA were summarized. Overall, the evidence suggested an association between treatment with statins and improvement of AAA.

1. Introduction

The dilation of abdominal aorta causes abdominal aortic aneurysm (AAA) which is irreversible (Wang et al., 2018). Its prevalence is different in among different populations (Marcaccio and Schermerhorn, 2021). It seems that almost 1.9% to 18.5% males and 0% to 4.2% women suffer from AAA (Ullery and Hallett, 2018). The asymptomatic AAA can cause an undiagnosed AAA, its rupture and surgical emergency (Wang et al., 2018). Aortic rupture often results in sudden death, with the mortality rate above 50% even when the patient undergoes timely surgery (Aoki et al., 2007). Various factors such as hypertension, hypercholesterolemia, family history, male gender, smoking and age may play role in development of AAA (Pande and Beckman, 2008). The most important mechanisms in developing AAA involve inflammation, apoptosis, extracellular matrix (ECM) destruction by proteolytic enzymes, proteolysis and oxidative stress (Chen et al., 2016; Shah, 1997). Surgery is not useful for AAA which is <55 mm in diameter. There are also no well documented pharmacological therapies to reduce the progression rate and rupture risk of AAA (Ferguson et al., 2010). However, different studies investigated various compounds in animal models of AAA to find effective agents which might reduce the progression or prevent AAA. Small randomized controlled trials have reported that some medication such as roxithromycin (Vammen et al., 2001) and doxycycline (Baxter et al., 2020) could prevent AAA expansion.

Hydroxymethylglutaryl-coenzyme A reductase inhibitors (statins) are the most widely prescribed lipid-lowering medication worldwide. Although several new classes of lipid-modifying agents have been introduced in the past two decades (Kosmas et al., 2021; Sahebkar and Watts, 2013; Sahebkar and Watts, 2013), statins still are the mainstay drugs in the management of atherosclerotic cardiovascular disease. Such an indispensable role not only pertains to the conventional lipid-lowering effects, but also to numerous pleiotropic actions that are seemingly lipid-independent (Dehnavi et al., 2021; Shakour et al., 2020; Sohrevardi et al., 2021; Gorabi et al., 2021; Vahedian-Azimi et al., 2021; Khalifeh et al., 2021; Bland et al., 2022; Bahrami et al., 2018, 2020). In

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this context, some observational studies have statins slow down AAA growth. Since matrix metalloproteinases (MMPs) (Thompson and Parks, 1996), especially MMP-9, have the main role in degradation of aortic wall structures (McMillan et al., 1997), the beneficial effect of statins may be related to reduction of MMP activity (Wilson et al., 2005). In this review, we analyze the studies which have evaluated the relationship between AAA and statins.

2. Methods

The articles from different databases such as PubMed, Google Scholar, Science Direct, and Scopus (from 2000 to 2022) were extracted based upon the titles of the articles and the key words. The key words included: "abdominal aortic aneurysm", "statins", "matrix metalloproteinases", "MMP", "oxidative stress", "atherosclerosis" and "inflammation".

The inclusion criteria were: all studies which evaluated the effect of statins on AAA in animal, human, *ex vivo* or *in vitro* studies. The articles were limited to English language The reference lists of papers identified were also manually searched to find other potentially eligible articles.

2.1. Animal studies

The animal studies were summarized in Table 1. In a study, simvastatin was applied at a dose of 2 mg/kg in elastase-induced-AAA in wild-type or apoE-deficient mice for 14 days. The results showed that simvastatin decreased the development of AAA in both models of normocholesterolemic and apoE-deficient mice. Simvastatin caused a preservation of the structure of arterial wall, it decreased the expression of MMP-9 and increased the level of tissue inhibitor of metalloproteinases-1 (TIMP-1). The prevention of AAA by simvastatin was independent of its lipid-lowering effect (Steinmetz et al., 2005). In another study simvastatin or placebo were administered by gastric lavage in wistar rats with elastase-induced aneurysm before surgery. The infrarenal aorta was separated after 7 days. Simvastatin decreased the aneurysm diameter, it also decreased NF-KB, MMP-9 and oxidative stress. It suppressed some genes including those for interleukin 1, interleukin 4, inducible nitric oxide synthase, P-selectin, platelet-derived growth factor α, tumor necrosis factor, and several chemokines (Kalyanasundaram et al., 2006). In another study, two types of mice were used including those with functional Nrf2 (wild-type (WT) or with transcriptionally inactive form of Nrf2 (transcriptional knockout (tKO). Angiotensin-II was infused at a dose of 1000ng/kg/day by osmotic mini-pumps for 4 weeks. Simvastatin (20 mg/kg) was administrated by intra-gastric gavage 7 days before Ang-II treatment and continued to be administered for 28 days. Ang-II increased the blood pressure and caused vascular damage, inflammation, and oxidative stress which all had a role in development of AAA. Simvastatin decreased the formation of AAA by having effects on Ang-II in both genotypes and it decreased blood pressure in two types of mice. Ang-II increased the expression of VCAM1 (vascular cell adhesion molecule-1) and SELE (E-selectin) expression in tKO mice which was completely inhibited by simvastatin. Ang-II increased the reactive oxygen species in aortic wall while simvastatin did not modify the expression anti-oxidant enzymes (Kopacz et al., 2020). The model of AAA was induced in male *Apoe-/-* mice by osmotic minipumps injecting Ang-II for 28 days. Pravastatin (50mg/kg) was administrated by adding to drinking water for 8 weeks. After 28 days, Ang-II caused an enlarging of abdominal aorta diameter. Moreover, pravastatin increased the incidence of AAA, mortality and severity of AAA in Ang-II group. However, pravastatin promoted AAA in *Apoe-/-* mice. Pravastatin also increased MMP2, AMP-activated kinase alpha 2 (AMPKα2) and alpha protein 2 (AP-2α) in cultured vascular smooth muscle cells (VSMCs). The results of this study indicated that pravastatin promoted AAA formation through AMPKα2-dependent AP-2α activations and an increase of Ang-II-induced AAA occurred (Ma et al., 2017). In another study, the anti-AAA effect of atorvastatin against elastase-induced AAA in rats was evaluated. Atorvastatin caused a decrease of aneurysm diameter when compared with control group. It suppressed migration of macrophages to aortic wall one week after surgery, it prevented the expression of ICAM and MCP-1 which caused an inhibition of MMP12. It also increased the synthesis of collagen and elastin in the aortic wall. However, attenuation of AAA development by atorvastatin may be related to anti-inflammatory effect of this drug (Shiraya et al., 2009). In another study apoE-/- male mice received rosuvastatin (10mg/kg/day) and atorvastatin (20mg/kg/day) by drinking water for 1 week before starting to receive an Ang-II infusion. Ang-II caused AAA and a dilation of aorta diameter after 28 days. The findings of this research suggested that statins had no significant effects against AAA induced by Ang-II. However, their effects on atherosclerosis were different. Atorvastatin decreased atherosclerotic lesion areas and accumulation of lymphocytes. Atorvastatin also upregulated anti-inflammatory genes without any effect on inflammatory cytokines and serum lipids concentrations (Wang et al., 2011). When atorvastatin was applied in two models of aneurysm, including AAA induced by Ang II in ApoE−/− mice and CaCl2-induced AAA in C57 mice, atorvastatin was able to suppress the development of AAA in both models. Endoplasmic reticulum (ER) signaling pathway and inflammatory responses have a role in formation of AAA following Ang-II infusion. Atorvastatin caused a decrease of occurrence of AAA, which may be related to attenuation of ER stress signaling proteins, apoptotic cells, and the promotion of Caspase12 and Bax. It also reduced cytokines that play an important role in inflammation such as IL-6, IL-8 and IL-1β. In an *in vitro* study vascular smooth muscle cells and RAW264.7 were exposed to simvastatin and then after 1 h Ang-II was added for 24 h. Simvastatin inhibited apoptosis pathway and ER signaling in both cell lines (Li et al., 2017). In a study in which AAA was created by infusion of porcine pancreatic elastase and application of plastic cuff the atorvastatin group (1mg/kg/day) was compared with control group after 28 days. There was no difference between statin group and the group which was not treated with a statin. Atorvastatin has beneficial effects on post-operative histological feature of aortic elastin network, on protection of contractile fibers of vascular smooth muscle cell, a higher vasa vasorum density, as well as on prevention of intima and media thickening. Therefore, atorvastatin may inhibit the occurrence and reduce the further development of AAA (Houdek et al., 2013). A study showed that intravenous administration of nanoparticles of pitavastatin (containing 0.12mg/kg/week) in Ang-II-induced AAA in Apoe^{-} mice decreased AAA development, which was related to reduction of macrophage accumulation and MCP-1 expression. It decreased the activity of MMPs and elastin degradation (Katsuki et al., 2021) (Table 1).

2.2. Human studies

The *ex vivo* and clinical studies are shown in Table 2. In a study, the specimens of aortic aneurysm wall were isolated from 10 patients with AAA and aortic specimens were obtained from nine patients with aortoiliac occlusive disease as control for evaluation by immunohistochemical analysis. In one group the specimens were exposed to various concentrations of cerivastatin (0.001 to 0.1 mol/L) for 48 h. Cerivastatin reduced total and active MMP-9 in a dose dependent way by prevention of the activation of macrophages and neutrophils (Nagashima et al., 2002). The patients with large AAA were divided into two groups, one group received simvastatin at a dose of 40mg/kg/day for 3 weeks before surgery while the other group took placebo. During surgery, a section of aneurysm wall was separated and the level of MMP-9 was evaluated in both groups. The findings showed that statin therapy suppressed MMP-9 production suggesting that that statin therapy could be useful for the prevention or treatment of AAA (Evans et al., 2007). In another study, 63 patients without symptoms of AAA had selective surgery. 17 of them were treated with a statin before the surgery and the other with placebo. The sections of the aortic wall were isolated during the surgery and different types of MMP were evaluated. The results showed that statin

Table 1
Effect of statins on AAA in animal studies.

Type		Study design	drugs	Duration of study	dose	result	Ref.
In vivo	Animal study (rat)	Elastase-induced-AAA in normo cholesterolemic and apoE-deficient rats	Simvast atin	14 days	2mg/kg	Preservation of structure wall MMP-9 TIMP-1	(Steinmetz et al., 2005)
In vivo	Animal Study (rat)	Administration of statin by gastric lavage in elastase-induced-aneurysm before surgery	Simvastat in	Separation of aorta after 7 days	60mg/kg/day	Aneurysm diameter, NF- KB, MMP-9, oxidative stress, interleukin 1, interleukin 4	(Kalyanasundaram et al., 2006)
In vivo	Animal Study (mice)	Infusion of Ang-II for 4 weeks	Simvastat in	Administr ation of simvastatin by intra-gastric lavage for 5 weeks	20mg/kg	Blood pressure, VCAM and SELE	(Kopacz et al., 2020)
In vivo	Animal study (mice)	Infusion of Ang-II in Apo-E mice for 4 weeks	Pravastat in	Pravastatin was given via drinking water for 8 weeks	50mg/kg	incidence of AAA, mortality and severity of AAA	(Ma et al., 2017)
In vitro	Cell culture	Ang-IIinduced AAA in VSMCs for 24h	Pravastat in	The cells were exposed to pravastatin for 30 min	50μM	MMP2 AMPKα2 AP-2α	(Ma et al., 2017)
In vivo	Animal study (rat)	Infusion of elastase-induced AAA for 30min	Atorvast atin	Drug was given daily until harvest.	20mg/kg/day	MMP-12, MMP-2, MMP-3, MMP-9, MCP- 1 and ICAM	(Shiraya et al., 2009)
In vivo	Animal Study (mice)	Infusion of Ang-II- induced AAA in apo-e mice for 4 weeks	Rosuvast atin or Atorvast atin	Administratio n of drugs by drinking water for 5 weeks	Rosuvast atin (10 mg/ kg/ day) and atorvastat in (20mg/ kg/day)	These statins had not significant effects against AAA	(Wang et al., 2011)
In vivo	Animal study (mice)	AAA induced by Ang II in ApoE−/− mice for 28 days	Atorvast atin	Administrated by lavage for 5 weeks	20 or 30 mg/kg/day	Reduced ER stress signaling proteins, the number of apoptotic cells, and the activation of Caspase12 and Bax	(Li et al., 2017)
		CaCl2-induced AAA in C57 mice		Administrated by lavage for 7 weeks	20mg/kg/ day		
In vitro	Vascular smooth muscle cells (VSM CS) and Raw 264.7 cells	The cells were exposed to Ang-II for 24h	Simvasta tin	Added before to Ang-II exposure	0.1, 1 and 10 μmol/l	Inhibition of ER stress signal pathway and apoptosis dose dependently in both types of cells	(Li et al., 2017)
In vivo	Animal study	AAA was induced by infusion of porcine pancreatic elastase	Atorvast atin	28days	1mg/kg/da y	Atorvastain has no effect on diameter of aorta but has preventive effects on histopathologic al AAA	(Houdek et al., 2013)
In vivo	Animal study (mice)	Ang-II-induced AAA in Apoe^{-} mice	Pitavasta tin	Administrated by tail vein for 4 weeks	Administra tion of nanopartic les of pitavastati n (containing 0.12mg/k g/ week) intravenou sly	MMPs MCP-1 Macrophage accumulation	(Katsuki et al., 2021)

Abbreviations: Abdominal aortic aneurysm (AAA), Monocyte chemoattractant protein-1 (MCP-1), nuclear factor kappa B (NF-κB), matrix metalloproteinases (MMP), tissue inhibitors of metalloproteinases (TIMP), E-selectin (SELE), vascular cell adhesion molecule-1 (VCAM1), AMP-activated kinase (AMPK), alpha protein 2 (AP-2α), intercellular adhesion molecule 1 (ICAM), endoplasmic reticulum (ER).

treatment decreased the level of MMP-9 and MMP-3 when compared with placebo (Wilson et al., 2005). In a retrospective study 211 patients were divided into two groups – one treated with a statin and the other group did not receive a statin. The patients were followed up for one year. The study showed that the growth rate of diameter decreased in statin group when compared with non-statin group (Karrowni et al., 2011). Extensive aortic atheroma is common in AAA patients and it usually has an irregular appearance. In a retrospective study, statins were administrated to AAA patients. The comparison before and after statin administration showed that statins reduced the extensive aortic atheroma which was an effect that could be related to the pleiotropic effects of statins (Nemoto et al., 2013). A cohort study showed that AAA patients who had open surgery and received statins had beneficial effects concerning long-term survival and early mortality (Mathisen and Abdelnoor, 2017). A clinical trial showed that treatment with statins during the preoperative period caused better survival when compared with patients who did not take statins (O'Donnell et al., 2018). The specimens of aorta wall were obtained from patients during surgery and exposed to different concentrations of simvastatin. The results showed that simvastatin prevented NF-KB activation. Simvastatin also decreased the secretion of MMP-9, monocyte chemoattractant protein (MCP)-2 and epithelial neutrophil-activating peptide (CXCL5). However, anti-AAA effect of statins can be related to inhibition of Rac1/NF-κB pathway which causes suppression of MMP-9 and chemokine secretion in human AAA (Yoshimura et al., 2015). A meta-analysis of 11 observational studies based on 4647 AAA patients indicated that statin therapy prevents the growth of small AAAs (<55 mm in diameter) (Takagi et al., 2012). Another meta-analysis on 11933 AAA patients showed that statin therapy seemed to improve all-cause survival after AAA repair (Twine and Williams, 2011). In a study in which simvastatin or atorvastatin were administrated to AAA patients that used statins for at least 6 weeks and who had an open AAA repair. Both statins caused a decrease of NF-KB, inflammatory mediators such as IL-6 and MCP-1, cysteine protease, as well as macrophage-related markers e.g. cathepsin K and S. However, despite anti-inflammatory effects of statins, these drugs did not reduce AAA growth rate (van der Meij et al., 2013) (Table 2). Different studies have demonstrated that administration of statins in AAA patients can have positive effects and could reduce progression of AAA, rupture and perioperative mortality.

2.3. Potential mechanisms of action

AAA is a severe disease which can cause rupture and death if not treated. The important pathological process of AAA pathogenesis involves an increase of inflammation factors such as monocyte chemoattractant protein-1 (MCP-1) and infiltration of macrophages, activation

Table 2
Effect of statins on AAA in clinical and *ex vivo* studies.

Type	Study design	drugs	Duration of study	dose	result	Ref.
Ex vivo study	The aortic specimen was isolated from 10 patients with infrarenal AAA	Cerivastatin	48h	0.001-0.1 mol/l	MMPs Activation of macrophages and neutrophiles	(Nagashima et al., 2002)
Ex vivo study	During the surgery, a section of aneurysm wall was separated in patients with large AAA	Simvastatin	3 weeks before surgery	40mg/kg	MMP-9 in comparison with control group	(Evans et al., 2007)
Human study	211 patients were divided two groups. 136 patients in the statin and 75 patients in the non-statin group. AAA diameter in two groups was measured bye serial imaging surveillance. for one year	Statin users were identified as patients who were on any statin therapy at the initial imaging study. Non-statin users were identified as patients not on any statin during the entire study period.	One year	Not mentioned	The growth rate of diameter in statin group was lower than non- statin group	(Karrowni et al., 2011)
Human study	Contrast-enhanced computed tomography (CECT) was used to examine thoracic aortas of 29 patients (statin group; n = 22, non-statin group; n = 7) with extensive atheromas	Pitavastatin (n = 7), atorvastatin (n = 7), rosuvastatin (n = 4), fluvastatin (n = 2), simvastatin (n = 1), and pravastatin (n = 1)	897 days	Not mentioned	This pilot study showed that the area of atheroma decreased after administration of statins, and the atheroma reduction ratio was significant (P <0.01).	(Nemoto et al., 2013)
Human study	A retrospective cohort study was performed to compare early and total mortality for all patients treated for AAA with open surgery who were taking statins compared to those who were not.	Statin therapy	The median follow-up was 3.93 years,	Not mentioned	This retrospective cohort study showed a significanlyt beneficial effect of statin use on early and long-term survival for AAA patients treated with open surgery.	(Mathisen and Abdelnoor, 2017)
Human study	37950 patients with AAA repair (29,257 endovascular and 8693 open) entered this study	Statin therapy	2.9 years	Not mentioned	Preoperative statin use was associated with higher adjusted 1-year (94% vs 90%) and 5-year (85% vs 81%) survival (P < .001) compared with those who were not taking a statin, whereas those who started a statin therapy postoperatively also had higher 1-year (94% vs 91%) and 5-year (89% vs 81%) survival (P < .001).	(O`Donnell et al., 2018)
Ex vivo study	The specimens of aorta wall were obtained from patients during surgery and exposed to different concentrations of simvastatin	Simvastatin	between 48 and 96 h	10 μM	NF-KB activation MMP-9 MCP-2	(Yoshimura et al., 2015)
Human study	Twelve cohort studies including 11933 AAA patients were reviewed	Statin therapy	-	Any dose of statin therapy	Statin therapy seemed to improve all-cause survival after AAA repair	(Twine and Williams, 2011)
Ex vivo study	An observational study was done in patients who were not treated with a statin (control group, n = 25), who were treated with an intermediate dose (20 mg/day simvastatin or atorvastatin, n = 28) and high dose statin (40 mg/day simvastatin or atorvastatin, n = 10). Statins were administrated for at least 6 weeks and patients underwent an open AAA repair. Then aortic wall tissue was taken from the anterior-lateral aneurysm	Simvastatin or atorvastatin	At least 6 weeks	20 or 40 mg/day	Inflammatory Mediators: IL-6 and MCP-1, cysteine protease, macrophage- related markers e.g. cathepsin K and S did not reduce AAA growth	(van der Meij et al., 2013)

Abbreviations: Abdominal aortic aneurysm (AAA), Monocyte chemoattractant protein-1 (MCP-1), nuclear factor kappa B (NF-κB), Matrix metalloproteinases (MMP)

of matrix metalloproteinase (MMP), the vascular media is degenerated and elastic fibers are damaged (Daugherty et al., 2011). The mechanism by which statins might control AAA is unclear but there are some studies indicating probable mechanisms (Fig. 1).

2.4. Nrf2 pathway

In physiological condition Nrf2 exists in a complex with Keap-1 and in stress Nrf2 is released and causes antioxidant response element- (ARE-) mediated genes expression (Loboda et al., 2016). Nrf2 stimulates anti-oxidant genes and may have protective effect on VSMC. It also reduces pro-inflammatory mediators (Choi et al., 2015). The studies have reported that the deficiency of Nrf2 increased the expression of inflammatory mediators such as MCP1, IL6, and TNFα (Ruotsalainen et al., 2013) and contributed to AAA formation and rupture (Song et al., 2020). Therefore, increasing of Nrf2 expression can have role in prevention of AAA. The activity of Nrf2 is reduced in an age-dependent way and it can have a role in development of diseases such as AAA (Kloska et al., 2019). Activation of Nrf2 can have beneficial effect on AAA (Kloska et al., 2019). The studies have reported protective effect of rosuvastatin in atrial fibrillation by activation of Akt/Nrf2/HO-1pathway (Yeh et al., 2015). Atorvastatin reduced Ang-II induced oxidative stress by regulation of Nrf2 which might additionally explain the role of Nrf2 in AAA (Fig. 2) (Ma et al., 2014).

2.5. HO-1 pathway

Hem-oxygenase (HO-1) as a cytoprotective enzyme has different

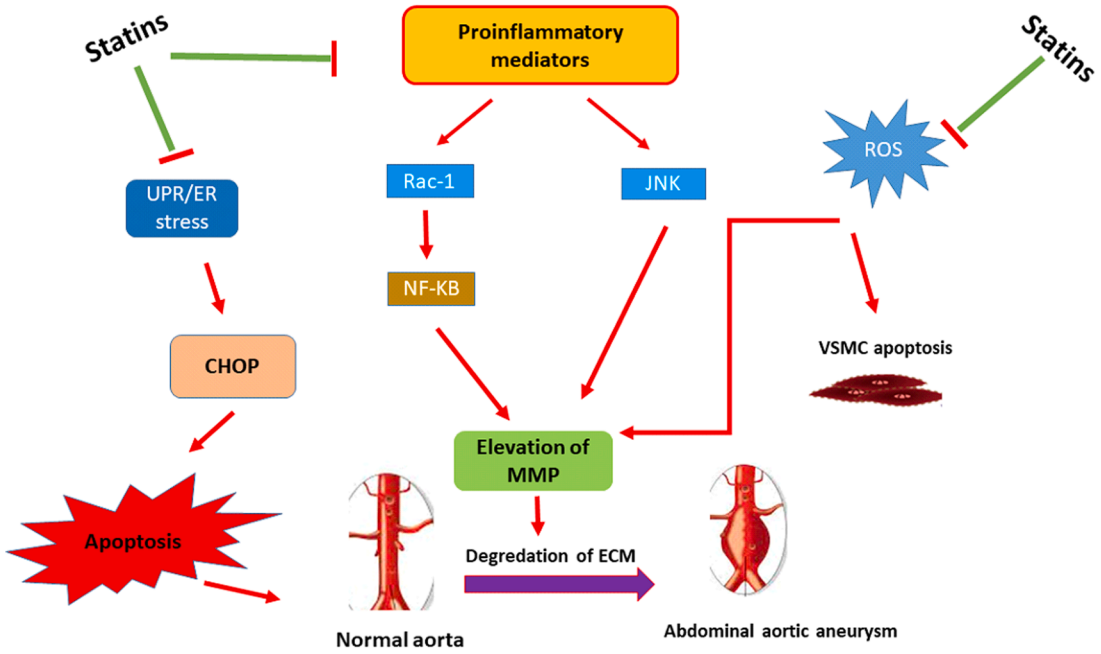

Fig. 1. Effect of statins on various pathway signaling to reduce development of AAA. Vascular smooth muscle cell (VSMC), Jun N-terminal kinases (JNK), (Rac-1), Nuclear factor-KB (NF-KB), Extracellular matrix (ECM), Unfolded protein response (UPR), Endoplasmic reticulum (ER), C/EBP homologous protein (CHOP), Reactive oxygen species (ROS).

properties such as immunomodulatory, anti-inflammatory, anti-apoptotic, anti-proliferative, anti-oxidant, and effects on vascular cells (Araujo et al., 2012). The studies have reported that the decrease of HO-1 expression might have a role in development of AAA (Azuma et al., 2016). In porcine pancreatic elastase (PPE)-induced AAA model in HO-1 heterozygous mice, deficiency of HO-1 caused development of AAA and an increase of pro-inflammatory cytokines in macrophages such as MCP-1, TNF-α, IL-6 and IL-1-β while the level of anti-inflammatory factors including TGF-β and IL-10 decreased (Azuma et al., 2016). Rosuvastatin in low doses suppressed AAA progression in an AAA model by inducing HO-1 expression in aortic tissue even in the absence of lipid lowering. (Azuma et al., 2016). Some other studies have reported that treatment with statins increases the expression of HO-1 in heart and lung tissues (Hsu et al., 2006; Lee et al., 2004). The increase of HO-1 causes a

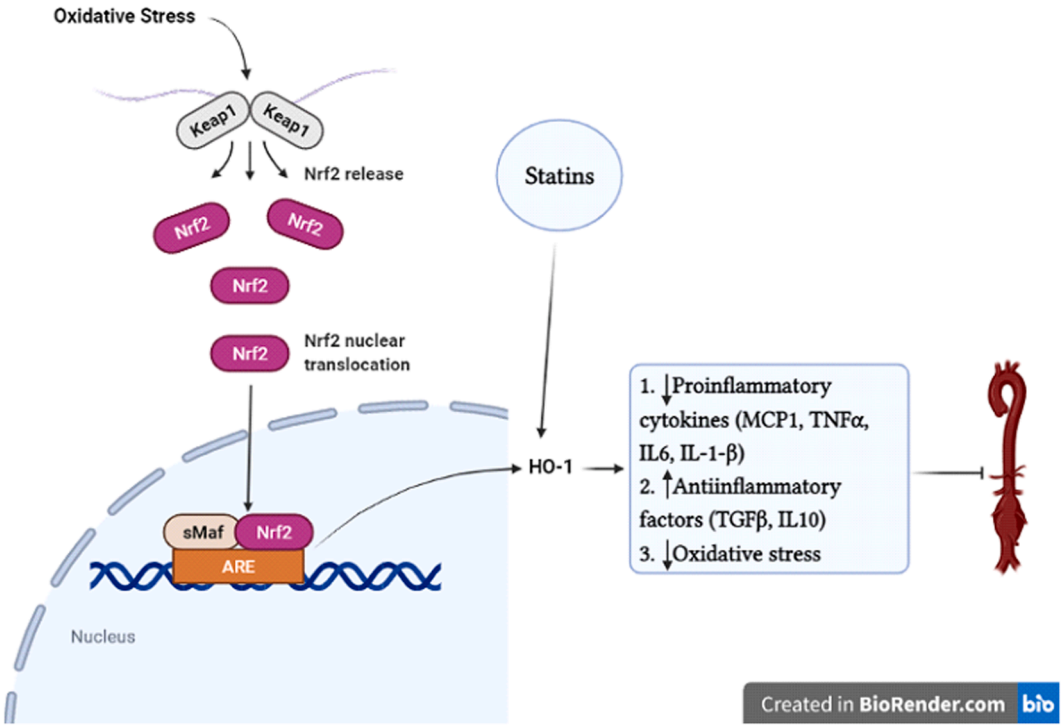

Fig. 2. Effects of statins on Nrf2/HO-1 signaling pathway to reduce AAA development. Nuclear factor erythroid 2–related factor 2 (Nrf2), Heme oxygenase-1 (HO-1), Kelch-like ECH-associated protein 1 (keap1), antioxidant response element (ARE), small musculoaponeurotic fibrosarcoma proteins (sMAF), monocyte chemo-attractant protein-1 (MCP-1).

decrease of inflammation and oxidative stress which are important factors in development of AAA.

2.6. Inhibition of MMP

In vivo and *in vitro* studies have indicated that overexpression of MMPs 1, 3, 8, 9 and 13 might have a role in progression and rupture of AAA (Sakalihasan et al., 1996; Crowther et al., 2000). The studies have reported that statins inhibit MMP expression in atherosclerotic lesions (Molloy et al., 2004) and AAA (Wilson et al., 2005; Nagashima et al., 2002). Simvastatin reduced MMP-9 and TIMP-1 (Steinmetz et al., 2005; Kalyanasundaram et al., 2006), atorvastatin had effects on prevention of MMP-12 via inhibition of ICAM-1 and MCP-1 expression (Shiraya et al., 2009), and cerivastatin decreased the level of MMP-9 in human organ culture system (Nagashima et al., 2002).

2.7. Anti-oxidant effects

Reactive oxygen species (ROS) and overexpression of pro-oxidant enzymes have an important role in development of human aortal aneurysm (Miller et al., 2002). ROS have an effect on c-Jun N-terminal kinase (JNK) and nuclear factor kappa B (NF-κB) (Diehm et al., 2007). Simvastatin prevents free radicals formation, TNFα production and elevation of anti-oxidant capacity by inhibition of NF-KB (Piechota-Polanczyk et al., 2012). The expression of inducible nitric oxide synthase (iNOS) has a role in formation of aneurysm in animal models (Lee et al., 2001; Johanning et al., 2002) and humans (Zhang et al., 2003). Simvastatin has role in prevention of of AAA by downregulation of iNOS expression (Kalyanasundaram et al., 2006). Therefore, one of the anti-AAA mechanisms can be inhibition of iNOS (Johanning et al., 2002).

2.8. Synthesis of ECM

The extracellular matrix (ECM), with collagen type I and elastin are important components of the aortic wall. The degradation of ECM proteins, especially elastin and collagen, can initiate AAA (Adams et al., 2021). The studies have shown that pro-inflammatory factors activate enzymes, which have an important role in degradation of ECM such as MMP 2 and 9 while they decrease lysyl oxidase (LOX) which increases the expression of ECM synthesis (Hellenthal et al., 2009). Statins may have effects on ECM remodeling by inhibition of MMPs.

2.9. Decreasing of TNF-α

The level of TNF-α is increased in patients with AAA and inhibition of TNF-α has an important role in preventing aneurysm formation (Xiong et al., 2009). Simvastatin decreased TNF-a, IL-6 and IL-1b in patients with hypercholesterolemia (Krysiak et al., 2011). It also reduced inflammatory factors in rat model of cardiopulmonary bypass (Shen et al., 2010). Simvastatin attenuated different interleukins (IL-4,5, 6,8 and 10), TNF-β and INF-γ in AAA. It also prevented the recruitment of T lymphocytes and macrophages in aortic wall (Hurks et al., 2010).

2.10. Regulation of endoplasmic reticulum (ER) stress

Endoplasmic reticulum (ER) stress signaling can cause a dysfunction of tissues and cells (Wang and Kaufman, 2012). Studies have shown that ER stress has an important role in development of heart failure, atherosclerosis and other cardiovascular diseases by activation of C/EBP homologous protein (CHOP) - which causes inflammation and apoptosis (Hotamisligil, 2010, 2010). Recent studies have shown that ER stress might be one of the mechanisms which play a role in AAA progression (Li et al., 2017). Yuanyuan et al. have reported that the suppression of AAA development by statins may be related to attenuation of ER stress signaling and ER stress-associated apoptosis as well as inflammatory response (Li et al., 2017). Simvastatin prevents the ER stress associated apoptosis signaling pathways in VSMC and RAW264.7. Atorvastatin reduces Ang-II-induced AAA in mice by suppression of ER stress pathway (Li et al., 2017). Statins suppressed the inflammation and apoptosis in the aorta by down-regulation of the PERK-p-EIF2α-CHOP associated ER stress signaling pathway (Li et al., 2017).

3. Conclusion

Several studies on animal models as well as on patients have reported that a relationship exists between treatment with statins and progression of AAA. Most statins decrease or prevent AAA by different mechanisms such as regulation of ER, anti-oxidantion, synthesis of ECM, inhibition of MMPs, attenuation of TNF-α, NF-κB and other mechanisms. Because of beneficial effects of statins in cardiovascular disease, their low cost and relative safety of statins, they may be appropriate candidates to be prescribed by physicians in AAA patients. Of course, different effects of statins on AAA may be related to different types of statins, doses, duration of treatment and different AAA models.

Data availability

No data was used for the research described in the article.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

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