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Doxycycline as an Important Metalloproteinases Inhibitor and Regulator: A Systematic Review

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Abstract

Introduction: Spontaneous coronary artery dissection (SCAD) may be a predictor of fibromuscular dysplasia (FD). There is a marked predominance in females, from 75.0 to 100.0% of the cases, with an average age between 30 and 55 years. Thus, the pathogenesis of FD can occur due to the fragmentation of elastic fibers that are degraded by matrix metalloproteinases 2 and 9 (MMP2, MMP9). Thus, the subtherapeutic use of doxycycline is highlighted, which is a tetracycline capable of inhibiting MMP activity regardless of its antimicrobial action.

Objective: Therefore, the present work carried out a systematic review of the main results of the inhibition and regulation of metalloproteinases by the use of the drug doxycycline.

Methods: The present study was a Case Report followed by the Systematic Review. The data sources and search strategy were PUBMED, EMBASE, OVID AND COCHRANE LIBRARY.

Results and conclusion: Doxycycline is considered the most potent and non-selective MMP inhibitor, when in subantimicrobial concentrations. Studies have suggested that doxycycline may reduce the increase in MMP-2 activity in resistance and conductance arteries, thus attenuating ventricular remodeling after myocardial infarction by decreasing the activity of MMP-2 and MMP-9. In addition, doxycycline appears to stabilize atherosclerotic plaques by inhibiting MMP in carotids, in addition to reducing the production of MMP-2 by vascular smooth muscle cells.

Keywords

Spontaneous coronary artery dissection; Fibromuscular dysplasia; Matrix metalloproteinases 2 and 9; MMP inhibitor; Doxycycline

Introduction

Spontaneous coronary artery dissection (SCAD) may be a predictor of fibromuscular dysplasia (FD) [1,2] that affects Caucasian, lean, 15- to 50-year-old women with no history [2]. There is a marked predominance in females, from 75.0 to 100.0% of the cases, with an average age between 30 and 55 years, and some studies have also identified this lesion in older postmenopausal women [3]. In this context, SCAD is a non-traumatic event generated by the segmentation of the coronary artery wall, creating a false light [1-3]. It is an infrequent cause of acute coronary syndrome (unstable angina) and sudden death. As its pathological mechanism is poorly understood, it is only known that SCAD is associated with the vascular system, inflammatory processes and vasculopathies, and fibromuscular dysplasia (FD) is the main one, with tortuosity being the main morphological sign [4]. Thus, the pathogenesis of FD can occur due to the fragmentation of elastic fibers that are degraded by matrix metalloproteinases 2 and 9 (MMP2, MMP9) [5]. However, the role of MMPs and their inhibitors in the pathogenesis of FD remains completely unexplored, being this the main information gap, and more clinical studies are needed to better understand the relationship of these enzymes and the involvement of coronary and other vessels [6,7]. Within this, it is known that the main predictors of this enzymatic breakdown may

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be postpartum periods, multiparity, tissue disorder, hormone therapies (use of anti-conception), use of certain illicit drugs, physical stress and emotional stress. In smaller proportions, it is associated with disorders such as Marfan, Ehlers-Danlos and Horner Syndromes [8-11].

As the pathophysiological control of the action of MMPs is still unclear, SCAD treatment remains in the decision to use invasive or non-invasive methods, through the analysis of clinical and angiographic factors that include the site of dissection, number of vessels affected, and condition hemodynamic in hospital evolution [12]. As an example, coronary angioplasty with stent implantation is able to restore flow, alleviate symptoms and treat dissection, but has a 65,0 % success rate. Coronary artery bypass surgery is reserved for multivessel SCAD and in trunk dissections. In addition, there are no studies evaluating long-term drug treatment [12-14]. In this context, several recent studies have shown that inhibiting these proteases can be an important therapeutic strategy for the treatment, for example, of arterial hypertension and its deleterious consequences. Thus, the subtherapeutic use of doxycycline is highlighted, which is a tetracycline capable of inhibiting MMP activity regardless of its antimicrobial action [15]. In this sense, doxycycline is the only MMP inhibitor approved for clinical use by the FDA (US Food and Drug Administration) in a "subantimicrobial" dose, that is, in doses that produce plasma concentrations lower than those required for its antimicrobial action [16,17]. Thus, the use of doxycycline has demonstrated beneficial effects in the treatment of other diseases in which MMP play pathological roles, such as abdominal aortic aneurysm [18], acute myocardial infarction [19] and rectal cancer [20]. Therefore, the present work carried out a systematic review of the main results of the inhibition and regulation of metalloproteinases by the use of the drug doxycycline.

Methods

Study Design

The present study was followed by the Systematic Review. After literary search criteria using the MeSH Terms (Spontaneous coronary artery dissection. Fibromuscular dysplasia. Matrix metalloproteinases 2 and 9. MMP inhibitor. Doxycycline) that were cited in the item below on "Search strategies", a total of 85 studies were compared and submitted to the eligibility analysis and, after that, 32 studies were selected, following the systematic review rules – PRISMA (Transparent reporting of systematic reviews and meta-analyzes-http: //www.prisma-statement.org/).

Data sources and search strategy

PUBMED, EMBASE, OVID AND COCHRANE LIBRARY databases were searched for analysis of the "risk of using anabolic steroids in occlusion of arteries" in the literature. Also, a combination of the keywords with AND and the Boolean operator "NOT" was used. The title and abstracts were examined in all conditions.

Study selection and risk of bias in each study

Two independent reviewers (1 and 2) performed research and study selection. The data extraction was performed by reviewer 1 and fully reviewed by reviewer 2. A third investigator decided some conflicting points and made the final decision to choose the articles. Only studies reported in Portuguese and English were evaluated. The COCHRANE instrument was adopted to assess the quality of the included studies.

Risk of bias

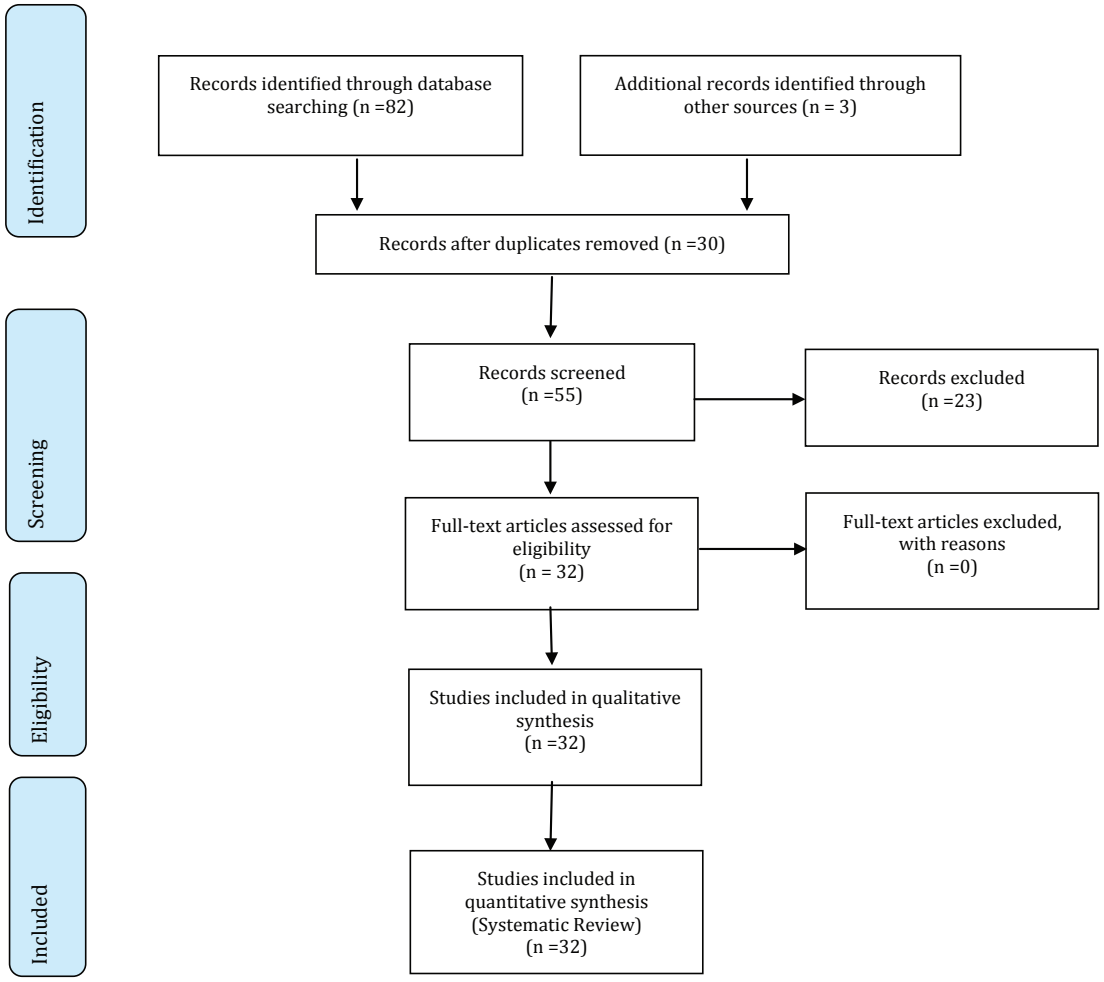
Considering the Cochrane tool for risk of bias, the overall evaluation resulted in 3 studies with a high risk of bias and 1 studies with uncertain risk. The domains that presented the highest risk of bias were related to a number of patients and risk factors related to the use of doxycycline. Also, the absence of the source of financing in 3 studies. Further, 2 studies did not disclose the information on the conflict of interest statement (Flow Chart).

Results and Discussion

MMP is a family of zinc and calcium-dependent endopeptidases that are secreted or anchored in the cell membrane and are able to degrade the multiple components of the extracellular matrix [1]. MMP is often over expressed or highly activated in a number of human diseases. Due to the important role of MMP in human diseases, many MMP inhibitors have been studied, in particular, doxycycline, being the only inhibitor approved by the FDA [2]. In this sense, MMP-2 plays an important role in the pathogenesis of type A aortic dissection (AD). One study analyzed the association of 3 single nucleotide polymorphisms in the MMP-2 gene with the risk of type A (AD) and aortic diameters. MMP-2 polymorphisms contributed to type A susceptibility. MMP-2 nucleotide gene associate with AD size which could be targeted for new drug therapies [13]. MMP tissue inhibitor imbalances, the TIMP may lead to aortic wall failure. Total MMP-1, total MMP-9, and active MMP-9 levels were higher and total MMP-2 levels were lower in dissection tissue than in control tissue. The ratio of MMP-9 to TIMP-1 and the ratio of active to total MMP-2 were higher. The ratio of MMP-2 to TIMP-2 was lower in dissection tissue. Patients had a higher ratio of plasma-active to total MMP-9 than controls. Age and hypertension associated with increased MMP levels. Several MMP increased levels and increased MMP-to-TIMP ratios in aortic tissue suggested an environment favoring proteolysis. This may promote progressive extracellular matrix destruction and medial degeneration after aortic dissection. An elevated active-to-total MMP-9 ratio in plasma may be a biomarker for an end-stage aneurysm in patients with the chronic thoracic aortic disease [13-15].

In this context, doxycycline is considered the most potent and non-selective MMP inhibitor [16]. Although tetracyclines are Zn2+ chelators [17], the primary mechanism of inhibition of MMP by doxycycline is unclear. However, it has been proposed that doxycycline can bind close to Zn2+ at the catalytic site and break the bond between that ion and calcium, thus blocking the active site and inhibiting MMP activity [18-21]. Studies suggest that doxycycline may significantly reduce the increase in MMP-2 activity in resistance and conductance arteries, thus attenuating ventricular remodeling after myocardial infarction [22,23] by decreasing MMP-2 and MMP activity -9 [24]. In addition, doxycycline appears to stabilize atherosclerotic plaques by inhibiting MMPs in carotids [25], and may also reduce the production of MMP-2 by vascular smooth muscle cells. This may be due to the decrease in mRNA stability for MMP [26]. Doxycycline has also been shown to decrease the degradation of the extracellular matrix in abdominal aortic aneurysms [21,27]. Castro et al. [14] showed that doxycycline can inhibit vascular remodeling induced by experimental arterial hypertension 2R1C in rats, using doses that would be considered very large (30 mg/kg/day), at least in comparison with the standard antimicrobial dose of doxycycline used in humans. In fact, the use of high doses of doxycycline administered in humans, in order to inhibit MMP, could lead to the development of bacterial resistance, which could make it difficult to treat certain bacterial infections, in addition to causing other types of adverse effects. Thus, in our laboratory, the effect of doses lower than 30 mg/kg/day of doxycycline on vascular changes associated with experimental hypertension 2R1C [28] was evaluated. We found that doxycycline, 30 mg/kg/day, decreased MMP-2 levels in the aorta, reversed endothelial dysfunction, in addition to attenuating the vascular changes found in 2R1C hypertensive rats. However, doses of 3 and 10 mg/kg/day did not produce such effects, suggesting that doses of doxycycline below 30mg/kg/day do not attenuate the vascular changes found in the 2R1C hypertension model [28].

In this sense, human studies should be carried out to test the hypothesis that low doses of doxycycline inhibit cardiovascular changes associated with arterial hypertension. Thus, it can be concluded that MMPs play an important role in the development of changes associated with experimental hypertension 2R1C, especially



Flow Chart: Cochrane tool for risk of bias

when participating in pathological vascular remodeling. Inhibiting such proteases can become an important therapeutic strategy for the treatment of vascular changes associated with arterial hypertension [28]. In animals, pre-eclampsia manifests itself as maternal hypertension and fetal growth restriction. MMPs are involved in hypertension and doxycycline lowers blood pressure by inhibiting MMPs. In addition, excessive levels of MMP and reduced nitric oxide (NO) bioavailability have been linked to preeclampsia. Thus, the involvement of MMP in hypertension in pregnancy-induced by the methyl ester of Nω-Nitro-L-arginine (L-NAME) in rats was analyzed. For this purpose, zymographywas performed to assess the activity of MMPs -2 and -9 in the placenta, uterus and thoracic aorta, systolic blood pressure, fetal placental development, and NO metabolites. Plasma antioxidant capacity, plasma levels of FMS soluble tyrosine kinase-1 (sFlt-1) and placental growth factor (PLGF) were also examined. Doxycycline prevented hypertensive pregnancy and significant reductions in the number of puppies induced by L-NAME. Low NO bioavailability was found in hypertensive rats treated (or not) with doxycycline [28].

The increased activity of placental MMP-2 and uterine MMP-9 and MMP-2 were alleviated by doxycycline. The activity of MMP-2 of the thoracic aorta did not change after hypertension. Increases in PLGF have been found with concomitant reductions in sFlt-1 levels with doxycycline treatment. In addition, plasma antioxidant capacity has been improved with doxycycline. In addition, elevations in plasma antioxidant capacity have been observed in hypertensive rats treated with doxycycline [29]. The cardiopulmonary bypass (CPB) applied during myocardial revascularization promotes inflammation, the generation of reactive oxygen species (ROS) and the positive regulation of MMP. All of these complications can lead to contractile dysfunction, restenosis, and early graft failure, restricting the long-term effectiveness of bridge grafts. Thus, a study investigated the effects of doxycycline on the generation of ROS, on the regulation of MMP and on contractile dysfunction induced by H2O2 in the human saphenous vein (HSV) grafts. HSV grafts (n = 7) were divided into four groups after removal of the endothelial layer by mechanical scratches and incubated with 10 μM H2O2 and / or 10 μM doxycycline for 16 hours. Untreated segments served as controls. Response curves were made to the concentration of noradrenaline (NA), potassium chloride (KCl), serotonin (5-HT) and papaverine. The superoxide anion and other levels of ROS were determined using chemiluminescence assays with lucigenin and luminol, respectively. The expression/activity of gelatinases (MMP-2 / MMP-9) was examined by gelatin zymography. MMP-13 expression was assessed by immunostaining/immunostaining. Incubation with H^2O^2 increased the superoxide anion and other levels of ROS. Doxycycline prevented these increases. H2O2 suppressed contractile responses to NA, KCl, and 5-HT. Doxycycline improved contractions for NA and KCl, but not for 5-HT. H2O2 or doxycycline did not alter papaverine relaxation. The expression of MMP-2 and MMP-13 increased with H2O2, but doxycycline inhibited

the regulation/activation of MMP-2. Low-dose doxycycline may have beneficial effects in increasing oxidative stress, regulating/activating MMP and contractile dysfunction in HSV grafts [30].

Still, another study found that doxycycline significantly reduced MMP-2 activity and pro-MMP-2 expression by 12Z and MMP-2 and -9 activity, as well as pro-MMP-2 and - 9 in primary endometriotic stromal cells. The percentage of 12Z cells invading a matrix coated with matrigel was reduced to 65 and 22% of the control after treatment with doxycycline at doses of 1 µg / mL and 10 µg / mL, respectively. In addition, a combination of progesterone and doxycycline showed an additive effect at low doses in reducing MMP-2 activity and pro-MMP2 expression in 12Z endometriotic cells. In conclusion, the MMP inhibitory characteristics of doxycycline in subantimicrobial doses can be further evaluated as an additional well tolerable therapeutic approach, in combination with progestins such as dienogest, in patients with infiltrative endometriosis with insufficient response to current medical treatment options [31]. Therefore, evaluating the activity of a specific subset of MMPs in human diseases, using clinically relevant imaging techniques, would be a powerful tool for early diagnosis and assessment of therapy effectiveness. Thus, a study provided an overview of the MMP subfamily and its structure and function. The potential use of diagnostic agents labeled with MMP inhibitors in clinical imaging techniques was also discussed, including positron emission tomography, single-photon emission computed tomography and optical imaging [32,33].

Conclusion

Doxycycline is considered the most potent and non-selective MMP inhibitor, when in subantimicrobial concentrations. Studies have suggested that doxycycline may reduce the increase in MMP-2 activity in resistance and conductance arteries, thus attenuating ventricular remodeling after myocardial infarction by decreasing the activity of MMP-2 and MMP-9. In addition, doxycycline appears to stabilize atherosclerotic plaques by inhibiting MMP in carotids, in addition to reducing the production of MMP-2 by vascular smooth muscle cells.

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Declaration of Potential Conflict of Interest

The authors declare no conflict of interest.

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