Association between use of aspirin or non-aspirin non-steroidal anti-inflammatory drugs and erectile dysfunction

A systematic review

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Abstract

Objective: There are various etiologies of erectile dysfunction (ED), including endothelial dysfunction, atherosclerosis, and chronic inflammation. Aspirin has a protective role against endothelial dysfunction and atherosclerosis, whereas all non-steroidal anti-inflammatory drugs (NSAIDs) are known for their anti-inflammatory properties. However, association between the use of aspirin or non-aspirin NSAIDs and ED is controversial. Therefore, we reviewed this relationship.

Methods: We systematically reviewed the pathophysiology of ED, physiological effect of prostaglandins, pharmacological action of NSAIDs, and clinical and basic research studies that evaluated the effect of aspirin or non-aspirin NSAIDs on ED.

Results: The research studies that assessed association between aspirin or non-aspirin NSAIDs are limited, and only 12 articles have been published. One clinical and three basic studies have claimed that aspirin or non-aspirin NSAIDs are beneficial for ED by preserving nitric oxide synthase impairment or penile blood hypercoagulability. One basic and two clinical studies considered them as risk factors because they interfered with prostaglandin production. By contrast, four clinical studies showed irrelevant results after controlling various medical indications. In addition, the mechanical effect of aspirin or non-aspirin NSAIDs on the nitric oxide pathway is still controversial.

Conclusions: The available research studies revealed that association between aspirin or non-aspirin NSAIDs and ED is controversial. Considering the high frequency of drug use, further clinical and basic investigations should be conducted to clarify their exact relationship.

Abbreviations: AA = arachidonic acid, CAMP = cyclic adenosine monophosphate, CCS = corpus cavernosum strips, COX = cyclooxygenase, CVD = cardiovascular disease, ED = erectile dysfunction, EF = erectile function, EFS = electrical field stimulation, eNOS = endothelial nitric oxide synthase, ICP/MAP = intracavernosal pressure/mean arterial pressure, iNOS = inducible NOS, nNOS = neuronal NOS, NO = nitric oxide, NSAIDs = non-steroidal anti-inflammatory drugs, PCa = prostate cancer, PGD2 = prostaglandin D2, PGE2 = prostaglandin E2, PGG2 = prostaglandin G2, PGH2 = endoperoxide, PGI2 = prostaglandin I2, PGs = prostaglandins, PKA = protein kinase A, TXA2 = thromboxane A2.

Keywords: Aspirin, chronic inflammation, endothelial dysfunction, erectile dysfunction, non-aspirin non-steroidal anti-inflammatory drugs

1. Introduction

Erectile dysfunction (ED) is defined as the inability to achieve or maintain sufficient penile erection for a satisfactory sexual performance. It is a common disease in middle-aged and elderly men, with an estimated prevalence rate of 25%–35%. ED is mainly considered an organic vascular disease, with similar risk factors, including hypertension, diabetes, and hyperlipidemia. All these factors reduce nitric oxide (NO) production, which is essential for normal erectile function (EF).

Bodies of evidences show that ED has been considered as an early indicator of CVD and that its severity is associated with heart disease severity. Considering its protective role against CVD, aspirin should be beneficial for ED. Meanwhile, low-grade inflammation processes or high circulating proinflammatory markers are also related to the ED process. Thus, aspirin or non-aspirin non-steroidal anti-inflammatory drugs (NSAIDs), with their anti-inflammatory ability, may also improve ED.

On the contrary, as vasodilative agents of prostaglandin I2 (PGI2) and prostaglandin E2 (PGE2), they have been used for penile rehabilitation by using SuperEnzyme of COX-2-linker-PGIS, aspirin or non-aspirin NSAIDs would deteriorate normal EF as they block cyclooxygenase (COX) activity to decrease these vasodilative prostaglandins (PGs).
ED is common in patients with prostate cancer (PCa), regardless of whether they received surgery or external beam radiation therapy. As inflammatory infiltration is found in the pathogenesis and progression of PCa, whether aspirin prevents PCa prevalence or progression is currently investigated. Thus, the effect of aspirin on PCa-related ED should be recognized. Although aspirin and non-aspirin NSAIDs consumption is tremendous (10–20 billions of aspirin has been taken annually to prevent CVD or atherosclerosis in the United States), we first systematically reviewed the potential role of aspirin or non-aspirin NSAIDs on ED progression, presenting a conclusion for concerned consumers.

2. PGs

As one of the most prevalent autacoids, PGs play an important role in regulating penile erection. Synthesis of PGs involves 2 steps. First, arachidonic acid (AA) released from cell membranes is converted to an unstable endoperoxide (PGG2) by PG endoperoxide synthase or COX. This is followed by the cleaving of peroxidase to peroxide and then the transformation to endoperoxide (PGH2). The unstable PGH2 are rapidly isomerized to biologically active end-products of PGI2, PGE2, prostaglandin D2 (PGD2), prostaglandin F2α (PGF2α), and thromboxane A2 (TXA2) by the corresponding synthase. PGs have incredible broad-spectrum effects and modulate almost every biological function.

In the penile erectile process, PGI2 and PGE1 can bind to the endothelial PGI receptor (IP) and PGE receptor (EP, mainly EP2/EP4). This will initiate adenylyl cyclase to increase intracellular cyclic adenosine monophosphate (cAMP) levels. The elevated cAMP can finally stimulate protein kinase A (PKA) to induce cascade of phosphorylation and inhibit myosin light chain kinase, with a result of trabecular smooth muscle relaxation and vasodilation. For this relaxant ability, PGI2 has been regarded as a valid candidate for ED treatment, whereas repeated intracavernous or intraurethral PGE1 injection can increase neuronal and endothelial NOS proteins to improve ED. PGD2 also produced modest relaxation of penile arteries via interaction with EP2 and other receptors. Except the relaxant PGs, PGI2 can also convert to TXA2 and PGF2α, which stimulate TXA2 and PGF2α receptors, respectively, to mediate contraction in human penile smooth muscle cells and arteries in various pathophysiological conditions. Meanwhile, hypercoagulability subsequent to the elevated TXA2 plays a key initiating role in aging impotence (Fig. 2).

3. NSAIDs

As the rate-limiting enzyme of PGs biosynthesis, COX was first purified from sheep seminal vesicles in 1976. Now, we recognize 2 distinct enzymes in humans, the constitutive COX-1 and inducible COX-2. They have a molecular weight of 70 to 71 kDa and an almost identical length, with 63% of its >600 amino acid content having similar sequences.

NSAIDs are a generic term for many chemically distinct drugs, including aspirin. Although having different family members and individual effects, all NSAIDs share a unifying mechanism of inhibiting COX activity to reduce PGs production, including the relaxant PGI2/PGE2/PGD2 and/or contractile TXA2/PGF2α.

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4. Beneficial factors

Endothelial dysfunction, chronic inflammation, and hypercoagulability play important roles in the ED process. As aspirin or non-aspirin NSAIDs prevent CVD or atherosclerosis, reduce hypercoagulability, increase NO bioavailability, and induce anti-inflammatory effects, it is reasonable to infer that they also improve ED. Whereas one clinical study and four basic studies evaluated this relationship and concluded with a beneficial result (Table 1).

Lithium carbonate, one of the few effective methods for maintenance therapy of bipolar affective disorder, has adverse effects on endothelium-mediated relaxation of corporeal tissue and leads ED through impairment of the NO pathway. The clinical study recruited lithium-related ED patients and found that aspirin improved EF in 85.4% of patients, which was significantly higher than the 19.7% of patients who showed improvement with placebo. In another rat study, indomethacin, another NSAID, reversed the lithium-related NO pathway deterioration and improved relaxant responses of corpus cavernosum strips (CCS). They speculated that aspirin or indomethacin improved the impaired endothelium-dependent relaxations in lithium-related ED by upregulation of the NO pathway. Another in vitro study also revealed that indomethacin strengthened the endothelium-dependent relaxation of human and rabbit CCS to bradykinin, acetylcholine, and substance P.
To decrease these vasorelaxation PGs[24] and interrupt  

improve ED. As aspirin or non-aspirin NSAIDs inhibit the COX  

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of CCS to acetylcholine and electrical  

al pressure (ICP/MAP) ratio, and improved relaxation response  

normalized the diminished intracavernosal pressure/mean arteri-  

proved that aspirin preserved impaired nNOS expression,  

protective effect was also observed in diabetic rat penis, which  

this assumption (Table 1).

Meantime, elevated TXA2 during erection contributes to  
hypercoagulability, which is essential to initiate penile vascular  
changes and impotence. With decreased TXA2 biosynthesis,  
aspirins delay intimal proliferation, prevents blood hypercoagu-  
ability, and improves arterial flow in the penis of chacma baboon.[23] As a result, penile atherosclerosis and aging  
impotence were prevented.[23,25] ED is also known for reduced  
ED in the NSAID group.[4] The adjusted OR decreased to 1.09  
(95% CI 1.06–1.13) and 1.38 (95% CI 1.29–1.47), respectively,  
after controlling the risk factors. However, the ORs were still  
significantly higher, and a dose-response relationship was  
observed.[4] Another Finnish study recruited 1126 men and  
controls of smoking, age, and some medical indications.  
The results showed that the relative risk of ED in the NSAID  
group was 1.8 (95% CI 1.2–2.6). Patients with (incidence density  
ratio [IDR]=2.0, 95% CI 1.2–3.5) or without arthritis (IDR=  
1.9, 95% CI: 1.2–3.1) who received NSAIDs showed increased  
incidence of ED as compared with those who did not use NSAIDs  
and had no arthritis. For the men with arthritis who did not  
receive NSAIDs, the risk was just slightly elevated (IDR=1.3,  
95% CI: 0.9–1.8).[5]

Meanwhile, a rat study showed that single-dose indomethacin  
significantly reduced the ICP/MAP ratio, whereas longer-term  
management significantly decreased the ratio at higher frequen-  
cies and even completely abolished erectile responses at low  
frequencies, with significantly total plasma NO level reduction  
observed.[25] It also significantly decreased the relaxation  
response of CCS to acetylcholine.[24] Moreover, diclofenac,  
another NSAID, also reduced erectile responses at low frequen-  
cies.[25]
Table 1

Study results.

| Journal (year) | Author/reference | Research object | Research type | Evidence level | Medicine          | Main result                                                                 |
|---------------|------------------|-----------------|---------------|----------------|--------------------|-----------------------------------------------------------------------------|
| BJU Int (2007) | Sadeghipour et al[26] | Lithium-treated SD rats | Basic | Basic | Indomethacin | Indomethacin significantly increased relaxant responses to acetylcholine in lithium-treated rat CCS. |
| J Urol (1992) | Azadbai et al[27] | Human and rabbit CCS | Basic | Basic | Indomethacin | Indomethacin significantly decreased the response to bradykinin, acetylcholine and substance P. |
| Br J Urol (1987) | Bonman et al[28] | Chacma baboons | Basic | Basic | Aspirin | Aspirin prevented penile blood hypercoagulability, which may delay penile atherosclerosis and ageing impotence. |
| Andrologia (2014) | Hafez et al[29] | Diabetic rats | Basic | Basic | Aspirin (Acetylsalicylic acid) | Aspirin preserved impaired NOG, normalized diminished IDR/MAP ratio, and improved relaxant response of diabetic rat CCS to acetylsalicylic acid and EFS. |
| J Urol (2011) | Gleason et al[30] | Kaiser Permanente Medical Care Program | Cohort study | 2b | NSAIDs | NSAIDs significantly improved moderate (OR: 1.09) and severe (OR: 1.38) ED. |
| J Urol (2011) | Stiri et al[31] | Tampere Aging Male Urological Study | Retrospective study | 3b | NSAIDs | NSAIDs increased ED incidence with arthritis (IDR: 2.0) or without (IDR: 1.9) than those who do not use NSAIDs and was free from arthritis. |
| World J Urol (2011) | Senber[32] | Health rats | Basic | Basic | Indomethacin | Single-dose indomethacin significantly reduced erectile response to electrical stimulation at all frequencies. Longer-term indomethacin abolished erectile responses at low frequencies and significantly reduced IDR/MAP at higher frequencies. It significantly reduced total plasma NO. |
| Irrelevance BJU Int (2016) | Patel et al[33] | Prostate Cancer Prevention Trial | Retrospective study | 3b | Aspirin | OR of severe ED reduced to insignificant 1.10 (P = 0.18). |
| BJU Int (2013) | Kapelian et al[34] | Boston Area Community Health Survey | Cohort study | 2b | Aspirin-containing medications | OR of ED reduced to insignificant 1.15 (95% CI: 0.72–1.85). |
| Am Heart J (2007) | Bohm et al[35] | Ontario/TRANSCEND | Retrospective study | 3b | Aspirin or clopidogrel | 89.2% Patients received aspirin or clopidogrel, which did not increase ED risk. |
| Int J Urol Nephrol (2008) | Bene et al[36] | Clinical Stroke patients | Retrospective study | 3b | Aspirin | Aspirin is the most common taken drug, the taken frequency is similar with ED (75%) and without (71%). |

BAP = bipolar affective disorder, CCS = corpus cavernosum strips, CI = confidence interval, CVD = cardiovascular disease, ED = erectile dysfunction, EFS = electrical field stimulation, IDR = intracavernosal pressure/mean arterial pressure, IDRI = incidence density ratio, nNOS = neuronal nitric oxide synthase, NSAIDs = nonsteroidal anti-inflammatory drugs, OR = odds ratio, ONTARGET/TRANSCEND = ONGoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial/Telmisartan Randomized Assessment Study in Aged-Risk Subjects with Cardiovascular Disease, RCT = randomized controlled trial. 
*Estimated with Oxford Centre for Evidence-Based Medicine.

6. Irrelevance

Aspirin or non-aspirin NSAIDs inhibit the production of vasodilative and vasoconstrictive PGs. Considering that PG2 concentration is low in penile blood during erection, prevention of PG2 synthesis is probably of minor importance in the erectile process.[37] Meanwhile, the relationship between PGE1 or PG2 and the NO signal pathway is still vague.[13] Thus, the protective or detrimental role of aspirin or non-aspirin NSAIDs on ED remains to be verified. Four large clinical investigations[21,9,5,12] have been performed and concluded an irrelevant relationship between aspirin or non-aspirin NSAIDs and ED (Table 1).

The Prostate Cancer Prevention Trial recruited 4726 men and summarized that administration of non-aspirin NSAIDs increased the risk of mild/moderate ED (OR 1.16; P = .02) and aspirin increased the risk of severe ED (OR 1.16; P = .03). As many NSAIDs indications such as arthritis, joint pain, muscle aches, hypertension, hyperlipidemia, coronary artery, and atherosclerotic disease directly cause ED, whether this association attributes to NSAID usage or medical disease is unclear. After a strict control of NSAID indications, the OR was reduced to insignificant values of 1.10 (P = .99) and 1.10 (P = .16).[10] The Boston Area Community Health survey included 2301 aged men and revealed that aspirin-containing medications were associated with higher ED risk in unadjusted analyses. However, OR was also reduced to an insignificant value of 1.15 (95% CI: 0.72–1.85) in the multivariable analyses.[38] A sub-study of ONTARGET/TRANSCEND trials evaluated the association between ED and current treatment in high-risk CVD patients. As a result, 89.2% of the patients received aspirin or clopidogrel, which
would not increase ED risk.\textsuperscript{12,19} Meanwhile, the Qatar trial of male stroke patients revealed that approximately 48.3\% of the patients claimed some degree of ED. Among the stroke survivors, aspirin was the most commonly used drug, while the use frequency of aspirin was similar for patients with (75\%) and those without ED (78\%).\textsuperscript{12} All these studies showed no association between aspirin or non-aspirin NSAIDs and ED.

7. NO and PGs

During penile erection, NO has been considered as the principal relaxing factor that causes cavernosal smooth muscle relaxation.\textsuperscript{24,28} Meanwhile, basal release of PGs has protective and relaxant roles in this process.\textsuperscript{12} NO and PGs also share considerable “cross talk” pathways.

First, NO activates COX activity to increase PGs production directly.\textsuperscript{12,23} As an antioxidant, NO removes superoxide to prevent COX autoactivation, it increases production of nitrosothiols\textsuperscript{12} and peroxynitrite\textsuperscript{34} to stimulate COX activity. Meanwhile, NO promotes post-transcriptional or translational level to increase COX-2 production,\textsuperscript{33} maintains prolonged COX gene expression,\textsuperscript{36} and acts on extracellular signal-related p38 kinase pathway and protein kinase to induce COX-2 activity.\textsuperscript{37} Thus, inhibited NO will prevent PGs expression.\textsuperscript{13}

In certain conditions, NO also inhibits COX-2 to reduce PGs production.\textsuperscript{38} Second, PGs interfere NOS expression and NO production. Elevated PGE\textsubscript{2} prevents inducible NOS (iNOS) mRNA expression and NO production by mediating cAMP levels in LPS-stimulated microglia cells.\textsuperscript{139} On the contrary, some COX inhibitors, such as aspirin or indomethacin, reduce intracellular Ca\textsuperscript{2+} levels to inhibit NOS activity in human platelets.\textsuperscript{140} Third, PGs and NO manage their own biosynthesis by regulating COX and NOS expressions.\textsuperscript{12,21} (Fig. 2).

After reviewing published literatures, we found that aspirin improved the deteriorated nNOS expression in diabetic rat penis\textsuperscript{29} and prevented blood hypercoagulability.\textsuperscript{23} Aspirin and indomethacin preserved impaired lithium-related NO pathway,\textsuperscript{23} whereas celecoxib significantly increased NO levels.\textsuperscript{23}

However, indomethacin reduced total plasma NO level.\textsuperscript{123} In conclusion, the interaction between NO and PGs biosynthesis occurs at multiple levels, but, its specific mechanism remains elusive.

8. Conclusion

Most clinical trials indicated an association between aspirin or non-aspirin NSAIDs and ED, but other studies reported inconsistent results, ranging from beneficial effects to marginal/moderate risk. These diverse clinical consequences may come from various study designs, population samples, dosages, or medical indications. In basic studies, aspirin improved EF in diabetic rats. Indomethacin preserved the lithium-related NO pathway, whereas celecoxib increased NO levels. Further clinical and basic studies must be performed to investigate the exact relationship between the use of aspirin or non-aspirin NSAIDs and ED.

Author contributions

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