



The Effect of Metformin on Male Reproductive Function and Prostate: An Updated Review

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Metformin is the first-line oral antidiabetic drug that shows multiple pleiotropic effects of anti-inflammation, anti-cancer, anti-aging, anti-microbia, anti-atherosclerosis, and immune modulation. Metformin's effects on men's related health are reviewed here, focusing on reproductive health under subtitles of erectile dysfunction (ED), steroidogenesis and spermatogenesis; and on prostate-related health under subtitles of prostate specific antigen (PSA), prostatitis, benign prostate hyperplasia (BPH), and prostate cancer (PCa). Updated literature suggests a potential role of metformin on arteriogenic ED but controversial and contradictory effects (either protective or harmful) on testicular functions of testosterone synthesis and spermatogenesis. With regards to prostate-related health, metformin use may be associated with lower levels of PSA in humans, but its clinical implications require more research. Although there is a lack of research on metformin's effect on prostatitis, it may have potential benefits through its anti-microbial and anti-inflammatory properties. Metformin may reduce the risk of BPH by inhibiting the insulin-like growth factor 1 pathway and some but not all studies suggest a protective role of metformin on the risk of PCa. Many clinical trials are being conducted to investigate the use of metformin as an adjuvant therapy for PCa but results currently available are not conclusive. While some trials suggest a benefit in reducing the metastasis and recurrence of PCa, others do not show any benefit. More research works are warranted to illuminate the potential usefulness of metformin in the promotion of men's health.

Keywords: Benign prostate hyperplasia; Erectile dysfunction; Men's health; Metformin; Prostate cancer; Reproductive function

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INTRODUCTION

Metformin is an oral anti-diabetic drug that has been recommended as the first-line therapy for patients with type 2 diabetes mellitus (T2DM) since 2012 [1]. It is now the most prescribed glucose-lowering drug and more than 150 million people in the world are prescribed metformin annually [2]. Metformin exerts

various beneficial effects beyond glucose lowering, including immune modulation, anti-atherosclerosis, anti-cancer, anti-aging, anti-microbia, and anti-inflammation [3,4]. Recently, by using the nation-wide database of the National Health Insurance in Taiwan, we also showed that metformin use is associated with a lower risk of hypertension [5], hospitalization for heart failure [6], hospitalization for atrial fibrillation [7], chronic

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obstructive pulmonary disease [8], varicose veins [9], hemorrhoid [10], dementia [11,12], nodular goiter [13], uterine leiomyoma [14], osteoporosis/vertebral fracture [15], and inflammatory bowel disease [16].

Metformin can cross the placenta and distribute to various tissues including salivary gland, tongue, stomach, intestine, colon, appendix, heart, muscle, liver, pancreas, kidney, adipose tissue, spinal cord, hypothalamus, pituitary gland, adrenal gland, thyroid, ovary, uterus, testes, and prostate [17-20]. Metformin is hydrophilic and, depending on cell types, it enters the cell *via* the plasma membrane monoamine transporter and the organic cation transporter (OCT) 1–3 and is excreted from the cell through OCT1 or multidrug and toxic compound extrusion type transporters (MATE1 and MATE2) [2]. Its serum half-life is approximately 5 hours and is excreted from the kidney without being metabolized [2]. It is rapidly transported and eliminated and may appear in the bladder 10 minutes after its oral intake [2]. It inhibits the activity of respiratory electron transport in mitochondria by binding to the mitochondrial complex I, leading to a decrease of adenosine triphosphate and thus activating the 5' adenosine monophosphate-activated protein kinase (AMPK) [2,17]. Metformin may also exert various activities *via* AMPK-independent pathways by modulating the expressions and actions of hormone, cytokines and growth factors [2,21].

Metformin has been researched for its potential usefulness for the treatment of polycystic ovary syndrome (PCOS) in women and is currently recommended as an adjunct to ovulation induction for the treatment of infertility in female patients with PCOS [22]. Metformin's benefits in men's health have been a focus of recent research, but more work needs to be done to confirm its usefulness in clinical practice. This article aims at reviewing the updated information published in related literature in the following two categories: men's reproductive health (penis and testes) and prostate-related health. Men's reproductive health will be discussed under three subtitles: erectile dysfunction (ED), steroidogenesis and spermatogenesis. Prostate-related health will be discussed under four subtitles: prostate specific antigen (PSA), prostatitis, benign prostate hyperplasia (BPH) and prostate cancer (PCa).

MEN'S REPRODUCTIVE HEALTH

Men's reproductive health and fertility are related to the erectile function of the penis and the testicular functions of steroidogenesis (testosterone synthesis) and spermatogenesis. Over the past decades, some studies have been conducted to investigate the effects of metformin on related issues and several review articles can be seen in the literature [17,22-24]. This topic will be discussed under the following three subtitles: ED, steroidogenesis (testosterone synthesis), and spermatogenesis.

1. Erectile dysfunction

In animals, metformin improved ED induced by angiotensin II in a rat model by restoring the expression of nitric oxide synthase and reversing the increased contraction and decreased relaxation in corpus cavernosum induced by angiotensin II [25]. Metformin also improved ED in rats with obesity and insulin resistance [26] and the combination use of metformin and icarisperide II (an active component with phosphodiesterase-5 inhibitory activity, derived from a Chinese medicine *Epimedium brevicornum*) improved ED in diabetic rats [27,28].

In humans, a randomized, double-blind, and placebo-controlled clinical trial had been conducted in Argentina in 30 non-diabetic men with insulin resistance who had poor response to sildenafil (100 mg) [29]. Metformin treatment for 4 months (1,700 mg/day, n=17) improved ED together with a reduction in body mass index and an improvement in insulin resistance [29]. This could be the only clinical trial available in the literature investigating the effect of metformin on ED. The positive result derived from this small trial should better be additionally confirmed.

The potential usefulness of metformin in ED with regards to its pathophysiological mechanisms has been reviewed by Patel et al in 2017 [30]. The authors concluded that metformin may potentially affect two of the three pathways involved in arteriogenic ED, *i.e.*, enhanced endothelium-dependent vasodilatation and sympathetic nerve activity attenuation, but metformin might not have a significant impact on the third pathway involving hypertension regulation [30]. However, the potential effect of metformin on ED *via* the third pathway is at least partly supported by our recent observational study that showed a significant

risk reduction of hypertension (hazard ratio [HR], 0.724; 95% confidence interval [CI], 0.681–0.769) in patients with T2DM who had been treated with metformin in comparison to patients who had never been treated with metformin [5]. Because hypertension is a well-recognized risk factor of atherosclerotic diseases and ED [31], an improvement in arteriogenic ED resulting from a reduced risk of hypertension and atherosclerotic diseases associated with metformin use is probable.

Another Iraqi cross-sectional human study that was not included in the review article by Patel et al [30] had a small sample size of 64 patients with T2DM and ED (34 patients treated with metformin and 30 patients treated with glibenclamide for their diabetes) in comparison to 27 healthy normal non-diabetic men as control [32]. The investigators concluded oppositely by showing that the group that used metformin had a lower level of testosterone, a reduction in sex drive and low testosterone-induced ED, while compared to a rise in testosterone level, sex drive, and erectile function in patients treated with glibenclamide [32]. Recently, the same group published another paper that might have included overlapping subjects and gave a similar conclusion [33]. Because of the incapability for a cross-sectional study design to answer a question of cause-effect relationship, the significant differences in baseline characteristics among the various subgroups and the lack of consideration of multivariate adjustment in data analyses, the interpretations of the results derived from these observational studies with small sample sizes should be cautious. Furthermore, it is worthy to note that these later observational studies showing a negative finding were conducted in diabetic men [32,33] but the result of a positive effect demonstrated by the earlier clinical trial was conducted in non-diabetic men with insulin resistance [29]. It remains to be answered whether the effects of metformin might differ between diabetes men and non-diabetes men.

Heart failure [34], atrial fibrillation [35], chronic obstructive pulmonary disease [36], osteoporosis [37], dementia [38], inflammatory bowel disease [39], and varicocele [40] have been associated with a higher incidence of ED in humans. Except for varicocele, our previous analyses supported a lower risk of all these morbidities among metformin users [6-8,11,12,15,16]. Although the effect of metformin on varicocele has not been studied, it is highly possible that metformin may reduce the risk of varicocele (another form of venous

dilatation involving the testicles) because metformin has been shown to reduce the risk of venous diseases of varicose veins [9] and hemorrhoid [10]. Therefore, metformin may potentially have a beneficial effect on ED by targeting not only the arterial system but also the venous system and related morbidities.

Insulin resistance, metabolic syndrome and obesity are associated with ED [41] and metformin use is always accompanied by an improvement in insulin resistance and lipid profiles and a reduction of body weight [42]. This may also partly explain the observation of an improvement in ED in patients who are concomitantly treated with metformin and sildenafil in non-diabetic men with insulin resistance in the clinical trial [29]. However, such a concomitant therapy for ED in patients who failed the monotherapy with phosphodiesterase type 5 inhibitor (PDE5i) is challenged by a recent systematic review article [43].

The effects of metformin on ED are summarized in Table 1. In summary, although a beneficial effect of metformin on ED is observed in animals, such a benefit in humans is under-studied and the findings remain controversial. Because psychosocial issues, comorbidities and clinical treatment with other medications may play important roles in the development of ED, these would surely complicate the interpretation of related human research. The usefulness of metformin as an adjunct to PDE5i for ED also awaits more investigation.

2. Steroidogenesis

An early study suggested that *in utero* exposure to metformin may lead to small testicular size and reduced number of Sertoli cells in male fetal Naval Medical Research Institute (NMRI) mice, possibly because of decreased testosterone secretion resulting from the increased production of lactate induced by metformin [44]. The investigators also showed that metformin decreased testosterone secretion and mRNA expression with increased lactate production in human and NMRI mouse organotypic cultures; and that human testes was more sensitive to metformin's effect than mouse testes [44]. However, a later human study that followed-up a cohort of boys born to mothers with gestational diabetes mellitus and having been treated with either metformin or insulin in an open-label, randomized clinical trial did not show any significant difference in pre-pubertal testicular size (mean age 60

Table 1. Summary of metformin's effects on men's reproductive health: erectile dysfunction (ED)

Studies/comments	Main findings
Animal studies	1. Metformin improves ED induced by angiotensin II in rats [25], in rats with obesity and insulin resistance [26] and in diabetic rats [27,28].
Human studies	1. A randomized, double-blind, and placebo-controlled trial conducted in Argentina suggests that metformin improves ED in non-diabetic men with insulin resistance [29]. 2. Cross-sectional studies conducted in Iraq suggest that metformin use in men with type 2 diabetes mellitus is associated with low testosterone-induced ED [32,33].
Author's comments	1. Metformin improves ED in rat models. 2. Human studies are rare and findings are not consistent. 3. Metformin may have benefits on arteriogenic ED by enhancing endothelium-dependent vasodilatation, attenuating sympathetic nerve activity and lowering blood pressure. 4. Metformin may also improve ED via an improvement of insulin resistance and metabolic syndrome and via a reduced risk of ED-associated comorbidities. 5. Interested readers may refer to recent review articles by Patel et al [30] and Alzain et al [23].

months at the time of receiving examination) [45].

In an animal study conducted in rabbits, metformin treatment to diabetic and non-diabetic animals resulted in a significant reduction in testicular weight, serum testosterone and sperm count, motility and viability [46]. However, animal studies conducted by the Malaysian group of Nna et al [47] showed that diabetes mellitus might induce fertility decline, dysregulation of steroidogenesis and abnormal spermatogenesis in the testes of male Sprague-Dawley rats. Furthermore, metformin (300 mg/kg body weight/day for 4 weeks) protected the testicular damages in male Sprague-Dawley rats by up-regulating anti-oxidant enzymes, down-regulating inflammation, and caspase-dependent apoptosis and by increasing immunoexpression of proliferating cell nuclear antigen (an indicator of proliferative activity of spermatogenesis) in the testes [48]. In another study by Nna et al [49], the beneficial effects of metformin on steroidogenesis and spermatogenesis would be more remarkable in diabetic rats when Malaysian propolis was co-administered. A study conducted by a separate Iranian group also suggested that co-administration of metformin and honey prevented damages to testes induced by diabetes in male Wistar rats by up-regulating diabetes-reduced insulin, luteinizing hormone (LH), follicular stimulating hormone (FSH), and testosterone [50].

Another collaborative group from Russia and India gave similar conclusions from studies conducted in male Wistar rats. They showed that metformin treatment for 4 weeks at 200 mg/kg/day normalized the steroidogenesis and spermatogenesis in the male rats which were induced diabetes by high-fat diet and low-

dose streptozotocin [51]. In another separate study the same group showed that 4-week metformin treatment at a dose of 120 mg/kg/day to male rats induced diabetes by high-fat diet and low-dose streptozotocin restored gonadotropin and leptin system (hyperleptinemia is associated with dysfunctions in the male reproductive system) and normalized testicular steroidogenesis and improved spermatogenesis [52].

In humans, as mentioned earlier, pre-pubertal testicular size was not affected in boys born to mothers with gestational diabetes mellitus treated either with metformin or insulin in an open-label, randomized clinical trial conducted in Finland [45]. Another early intervention study in Italy suggested that metformin treatment for 6 months (titrating from 850 mg qd to bid to tid) increased the serum level of testosterone and improved the LH pulsatility in obese individuals with metabolic syndrome [53]. However, more recent cross-sectional human studies conducted in Iraq concluded that metformin use in men with T2DM was associated with a lower level of testosterone, a reduction in sex drive and low testosterone-induced ED, in contrary to a rise in testosterone level, sex drive, and erectile function in patients treated with sulfonylurea [32,33]. Therefore, the effect of metformin on steroidogenesis of testosterone in human males is not conclusive and more research is needed.

The effects of metformin on steroidogenesis are summarized in Table 2. In summary, the small testicular size resulting from *in utero* exposure to metformin observed in an animal study can not be confirmed in a cohort of boys born to mothers with gestational diabetes mellitus. Although some animal studies suggested a

Table 2. Summary of metformin's effects on men's reproductive health: steroidogenesis

Studies/comments	Main findings
Cellular studies	1. Metformin decreases testosterone secretion and mRNA expression with increased lactate production in human and NMRI mouse organotypic cultures (human testes more sensitive than mouse testes) [44].
Animal studies	1. Male fetal NMRI mice exposed to metformin <i>in utero</i> may have small testicular size resulting from decreased testosterone secretion because of lactate production induced by metformin [44]. 2. Metformin significantly reduces testicular weight, serum testosterone and sperm count, motility and viability in rabbits [46]. 3. Metformin protects testicular damages in male Sprague-Dawley rats [48]; and the effects are more remarkable when co-administered with Malaysian propolis [49]. 4. Co-administration of metformin and honey up-regulates testosterone in male Wistar rats [50]. 5. Diabetes-induced abnormal steroidogenesis and spermatogenesis can be normalized by metformin in male Wistar rats [51,52].
Human studies	1. Follow-up of boys born to mothers with gestational diabetes mellitus treated with either metformin or insulin in an open-label, randomized clinical trial conducted in Finland: pre-pubertal testicular sizes are not different [45]. 2. An interventional study in Italy shows that metformin increases serum level of testosterone and improves luteinizing hormone pulsatility in obese individuals with metabolic syndrome [53]. 3. Cross-sectional studies conducted in Iraq show that metformin use in men with type 2 diabetes mellitus is associated with a lower level of testosterone [32,33].
Author's comments	1. Small testicular size as a result of <i>in utero</i> exposure to metformin is observed in an animal study, but not similarly seen in a human study. 2. Animal studies suggest a protective effect of metformin on testicular damages and a beneficial effect of metformin on steroidogenesis. 3. Except for one human cross-sectional study that suggests a potential harmful effect of metformin on testicular steroidogenesis, other human studies suggested a neutral or beneficial effect of metformin. 4. Interested readers may refer to review articles by Bertoldo et al [17], Ferreira et al [24], Faure et al [22], and Alzain et al [23].

NMRI: Naval Medical Research Institute.

restoration of testicular steroidogenesis in diabetic rats, scanty studies conducted in humans gave contradictory conclusions.

3. Spermatogenesis

A study conducted in diabetic and non-diabetic adult male Wistar albino rats suggested that metformin was neither genotoxic nor cytotoxic and may potentially protect hyperglycemia-induced genomic instability [54]. Another *in vitro* study suggested that metformin is not cytotoxic to Wistar rat Sertoli cells and can possibly be used safely in male diabetes patients of reproductive age [55].

In animals, metformin increases the viability of pig sperms after 24 hours storage [56] and improves the quality of frozen-thawed dog semen during cryopreservation [57]. However, inconsistent findings of metformin's effects on sperm number/concentration, morphology, motility, and viability have been noted in *in vivo* studies derived from various animal species including rat, rabbit and fish (reviewed by Faure et al) [22].

In diabetic and non-diabetic male Wistar albino rats, metformin seemed to have a beneficial effect on sperm

motility, count, and abnormalities [54]. This beneficial effect of metformin was supported by another recent study conducted in male Sprague-Dawley rats induced diabetes [47]. Co-administration of metformin and honey has also been shown to prevent damages to testes induced by diabetes in male Wistar rats by up-regulating diabetes-reduced insulin, LH, FSH, and testosterone [50]. More recent studies showed that metformin reduces testicular oxidative stress, inflammation, and caspase-dependent apoptosis in male Sprague-Dawley rats induced diabetes [48] and improves diabetes-induced subfertility/infertility in the rats (effect more remarkable when metformin was co-administered with Malaysian propolis) [49].

Metformin may also limit testicular ischemia/reperfusion injury in male Wistar rats [58] and injury on sperm production during testicular ischemia in male Wistar albino rats [59]. In other animal studies using rats, metformin reduces the injury to the reproductive system induced by diabetes or obesity [50,54,60]. More recent studies using obese male C57BL/6 mice fed with high-fat diet showed that metformin may improve fertility by alleviating blood-testis barrier damage in-

duced by oxidative stress [61] and may ameliorate the poor spermatogenesis and improve the semen quality through increased level of testosterone and its antioxidant capacity [62]. However, a negative effect on sperm concentration, mobility, and morphology has been reported in rabbits with alloxan-induced diabetes [46] and a neutral effect on sperm viability and mobility was observed in horses [63].

In humans, male patients with T2DM may have reduced sperm number and quality [22]. Metformin's effect on spermatogenesis has rarely been researched in humans. A small sample size clinical trial conducted in Iraq showed that metformin treatment for 12 weeks at a dose of 850 mg twice daily in 18 obese men with idiopathic asthenozoospermia was associated with a significant reduction of prolactin level, sperm count and sperm activity, but without significant changes in serum LH, FSH, estradiol, and testosterone after metformin treatment, suggesting a potentially harmful effect of metformin [64]. Because hyperprolactinemia may have a harmful effect on spermatogenesis [65], the role of the lowered prolactin level associated with metformin use on testicular function remained to be clarified. The investigators also speculated a potential harmful effect on spermatogenesis resulting from vitamin B12 deficiency that can be seen in approximately 20% to 30% of chronic metformin users [64]. However,

this study suffered from limitations of small sample size and without a control group.

Because insulin resistance, obesity, hypertension, and testicular inflammation are associated with poor sperm quantity and quality [22], metformin may at least have a beneficial effect on spermatogenesis through its effects on the improvement of insulin resistance, weight reduction, and metabolic control.

The effects of metformin on spermatogenesis are summarized in Table 3. Cellular and most animal studies, especially those conducted in rats and mice, suggested that metformin may have a beneficial effect on spermatogenesis, sperm motility, and sperm preservation. On the contrary metformin may have a potentially harmful effect as seen in a study conducted in rabbits and one human intervention trial.

As a summary for the potential roles of metformin on men's reproductive health, though not yet confirmed and somewhat controversial, metformin's potential usefulness in the treatment of infertility with regards to ED, steroidogenesis, and spermatogenesis are being explored.

PROSTATE-RELATED HEALTH

Prostate has the most abundant expression of OCT3 for the uptake of metformin [19,20]. Therefore, metfor-

Table 3. Summary of metformin's effects on men's reproductive health: spermatogenesis

Studies/comments	Main findings
Cellular studies	<ol style="list-style-type: none"> 1. Metformin is neither genotoxic nor cytotoxic and may potentially protect hyperglycemia-induced genomic instability in diabetic and non-diabetic adult male Wistar albino rats [54]. 2. Metformin is not cytotoxic to Wistar rat Sertoli cells and can possibly be used safely in male diabetes patients of reproductive age [55].
Animal studies	<ol style="list-style-type: none"> 1. Metformin increases the viability of pig sperms after 24 hours storage [56]. 2. Metformin improves the quality of frozen-thawed dog semen during cryopreservation [57]. 3. Metformin improves abnormalities in spermatogenesis and sperm motility in diabetic and non-diabetic male Wistar albino rats [54] and in diabetic male Sprague-Dawley rats [47]. 4. Metformin limits testicular ischemia/reperfusion injury in male Wistar rats [58] and injury on sperm production in male Wistar albino rats [59]. 5. Metformin reduces injury to the reproductive system induced by diabetes or obesity in rats [50,54,60]. 6. Metformin improves fertility in obese male C57BL/6 mice [61,62]. 7. Metformin has negative effects on sperm concentration, mobility and morphology in rabbits [46]. 8. Metformin has a neutral effect on sperm viability and mobility in horses [63].
Human studies	<ol style="list-style-type: none"> 1. An intervention trial conducted in Iraq: Metformin (850 mg bid for 12 weeks) may have a potentially harmful effect with regards to sperm count and activity [64].
Author's comments	<ol style="list-style-type: none"> 1. Metformin may protect against testicular injury and improve sperm quantity and quality in rats or mice. However, this can not be proven in a human clinical trial. 2. Metformin may theoretically exert beneficial effects on spermatogenesis through its improvement of insulin resistance, weight reduction and metabolic control. However, more human research is needed. 3. Interested readers may refer to review articles by Bertoldo et al [17], Ferreira et al [24], Faure et al [22], and Alzain et al [23].

min may potentially have an effect on prostate-related health. These issues will be discussed under the following subtitles: PSA, prostatitis, BPH, and PCa.

1. Prostate specific antigen

PSA is a widely used biomarker for PCa and has been recommended as a tool for the screening of PCa and as a follow-up marker for PCa therapy. A study investigating the effects of 14 commonly prescribed drugs on the expression of PSA mRNA in PCa cells (LNCaP cells) showed that except for a positive effect of betamethasone, all other drugs including metformin and insulin did not significantly affect PSA expression [66]. A later study using LNCaP cells also did not find an effect of metformin on PSA [67]. However, another study showed a significant reduction of PSA by metformin in two human PCa cell lines of LNCaP and C4-2 by up-regulating the protein level of small heterodimer partner-interacting leucine zipper resulting in an inhibition of androgen receptor function [68]. On the contrary, the study by Sarmiento-Cabral et al [69] showed that metformin did not affect PSA secretion in LNCaP cells, but might decrease PSA in 22Rv1 cells ($p=0.006$).

In humans, several epidemiological studies suggested that metformin use was associated with lower levels of PSA. A cross-sectional Canadian study showed that metformin use in patients with T2DM who were free from PCa was associated with lower levels of PSA in a dose-response pattern [70]. In another cross-sectional study that used the US National Health and Nutrition Examination Survey 2007 to 2008 cycle showed that metformin users in patients with T2DM and without a previous diagnosis of PCa had a lower level of PSA than non-metformin users (odds ratio [OR], 0.790; 95% CI, 0.666–0.938; $p=0.007$), although a dose-response relationship with duration of metformin use could not be similarly demonstrated [71]. It should be reminded that all these human studies are cross-sectional and therefore the cause-effect relationship could not be justified. Furthermore, it is not known whether such a reduced level of PSA associated with metformin use could be extended to an interpretation of a lower risk of PCa. A retrospective study that evaluated the risk of PCa in 2,032 patients (467 had diabetes and 1,565 were not diabetic) who underwent prostate biopsy in a hospital in Shanghai, China showed a significantly higher risk of PCa (especially high-grade PCa) in the diabetes pa-

tients even though they had a significantly lower level of PSA [72]. The investigators suspected a delayed detection because of the lower PSA levels in the diabetes patients that might have led to the high-grade PCa at diagnosis. However, another study conducted in Sweden did not support a masking effect of low PSA levels associated with anti-diabetic drugs [73]. Their analyses suggested a “potential detection bias due to fewer biopsies among men receiving anti-diabetic medications, which may explain the lower PCa risk in men with diabetes”. On the contrary, diabetes patients in the USA had an increased probability of receiving PCa screening according to an early study [74]. Another US retrospective study conducted in patients with PCa presented for radiation therapy suggested that metformin and statin users would have lower levels of PSA but these medications did not affect treatment outcomes [75].

An early multicenter phase 2 trial conducted in Switzerland in 44 non-diabetic men with metastatic castration-resistant PCa recruited from 10 Swiss centers suggested that metformin use at 1,000 mg twice per day might reduce PSA and cause disease stabilization after a treatment of 12 weeks [76]. Another early pilot single-arm intervention trial conducted in Canada showed that metformin use at 500 mg tid in patients with PCa was associated with a trend of PSA reduction (median level of PSA: pre-metformin 5.9 ng/dL and post-metformin 5.3 ng/dL, $p=0.08$) after a median duration of 41 days (18–81 days) [77]. This was also similarly observed in a recent intervention study from the USA that randomly administered either extended-release metformin 500 mg per day or placebo for 4 to 12 weeks to patients with PCa before prostatectomy [18]. The investigators failed to show a significant difference in PSA between the two assignments, even though the metformin group ($n=8$) showed a reduction of PSA in contrary to an elevation of PSA in the placebo group ($n=10$) [18]. It is not known whether the small sample sizes in these clinical trials could have led to the lack of significant difference after metformin use.

The effects of metformin on PSA are summarized in Table 4. In summary, cellular studies do not show consistent results of PSA following metformin treatment. Although some human observational studies supported a lower level of PSA associated with metformin use, this could not be confirmed by clinical trials with small sample sizes. More cellular, animal, and human (especially cohort observational studies or intervention

Table 4. Summary of metformin's effects on prostate-related health: prostate specific antigen (PSA)

Studies/comments	Main findings
Cellular studies	<ol style="list-style-type: none"> 1. Metformin does not affect PSA expression in LNCaP cells [66,67]. 2. Metformin reduces PSA level in a dose-dependent pattern in two prostate cancer cell lines of LNCaP and C4-2 by up-regulating the protein level of small heterodimer partner-interacting leucine zipper resulting in an inhibition of androgen receptor function [68]. 3. Metformin does not affect PSA secretion in LNCaP cells, but may decrease PSA in 22Rv1 cells ($p=0.006$) [69].
Human studies	<ol style="list-style-type: none"> 1. Cross-sectional observational studies suggest that metformin use in patients with type 2 diabetes mellitus and without prostate cancer is associated with lower levels of PSA in studies conducted in Canada [70] and in the USA [71]. 2. In a study conducted in China, among patients receiving prostate biopsy, diabetes patients have lower level of PSA but higher grade of prostate cancer than their non-diabetes counterparts [72]. 3. In a US retrospective study, metformin users in patients with prostate cancer presented for radiation therapy may have lower level of PSA, but this does not affect treatment outcomes [75]. 4. Interventional trials conducted in Switzerland [76], Canada [77], and the USA [18] showed a trend of PSA lowering (though not statistically significant) after metformin treatment for prostate cancer.
Author's comments	<ol style="list-style-type: none"> 1. Cellular studies do not show a consistent effect of metformin on PSA expression or secretion. 2. Metformin use may be associated with lower levels of PSA in humans with or without prostate cancer. However, its clinical implications are not clear.

trials) studies are required to clarify the effect of metformin on PSA expression and the potential clinical impacts of such an effect.

2. Prostatitis

Prostatitis can be clinically classified as asymptomatic prostatitis, acute bacterial prostatitis, chronic bacterial prostatitis, and chronic pelvic pain syndrome [78]. Major bacterial pathogens of prostatitis include *Enterobacteriaceae* (most common pathogen: *Escherichia coli*, which accounts for 65%-80%), *Enterococci* and sexually transmitted infections of *Chlamydia trachomatis* and *Mycoplasma genitalium* [78,79]. Animal or human studies investigating the effects of metformin on prostatitis are still lacking. However, metformin does exert anti-bacterial, anti-viral, and anti-fungal activities [3] and novel anti-microbial complexes containing metformin are being developed [4]. Therefore, metformin may reduce the risk of prostatitis through its anti-glycemic, anti-microbial, and anti-inflammatory actions.

In summary, whether metformin use can reduce the risk of bacterial prostatitis has not been researched but it is possible that metformin may reduce the risk of prostatitis through indirect effects of improving glycemic control and its anti-microbial and anti-inflammatory properties. Because chronic inflammation associated with prostatitis may predispose to the development of PCa [78,80-82], metformin's effect on prostatitis is an issue worthy of more in-depth investigation.

3. Benign prostate hyperplasia

A cellular study suggested that metformin inhibits the proliferation of benign prostate epithelial cells by reducing the expression of insulin-like growth factor 1 (IGF-1) and IGF-1 receptor and by regulating the cell cycle [83]. The authors also speculated a potential epigenetic effect of metformin on BPH in a later review article [84].

In male Sprague-Dawley rats, metformin attenuated BPH induced by testosterone [85] or by metabolic syndrome [86], probably through inhibiting the expressions of IGF-1 and IGF-1 receptor.

In humans, an earlier retrospective cohort study conducted in the USA did not find any association between thiazolidinediones or metformin (adjusted HR for metformin use, 0.99; 95% CI, 0.94–1.03) and BPH while compared to sulfonylureas [87]. However, a later retrospective cohort study conducted in Korea using the Health Insurance Review & Assessment Service suggested that diabetes patients who used metformin had a reduced risk of BPH progression indicated by the occurrence of prostatectomy during follow-up while compared to a group without T2DM (HR, 0.86; 95% CI, 0.77–0.96; $p=0.007$) [88].

Metabolic syndrome and its components of obesity, hyperinsulinemia, T2DM, dyslipidemia, and hypertension are significantly associated with BPH [89-93]. Therefore, metformin may not only reduce the risk of BPH *via* a direct effect on the prostate tissue, it may also act through indirect effects by correcting the

Table 5. Summary of metformin's effects on prostate-related health: benign prostate hyperplasia (BPH)

Studies/comments	Main findings
Cellular study	1. Metformin inhibits proliferation of benign prostate epithelial cell by reducing the expression of insulin-like growth factor 1 (IGF-1) and IGF-1 receptor and by regulating the cell cycle [83].
Animal studies	1. Metformin attenuates BPH induced by testosterone [85] or by metabolic syndrome [86] in male Sprague-Dawley rats, probably via a potential involvement of the suppression of the IGF-1 pathway.
Human studies	1. A retrospective cohort study conducted in the USA estimated a hazard ratio for BPH for metformin vs. sulfonylureas of 0.99 (95% confidence interval, 0.94–1.03) [87]. 2. A retrospective cohort study conducted in Korea estimated a hazard ratio for BPH progression indicated by the occurrence of prostatectomy for metformin use in patients with type 2 diabetes mellitus vs. non-diabetic control of 0.86 (95% confidence interval, 0.77–0.96; $p=0.007$) [88].
Author's comments	1. Cellular and animal studies support a potential beneficial effect of metformin on BPH, but results from human studies are not consistent. 2. Metformin may have a direct beneficial effect on BPH by inhibiting the IGF-1 pathway or an indirect effect via improving insulin resistance and metabolic syndrome. 3. Interested readers may refer to a review article by Wang and Olumi [84].

metabolic dysregulations in the various components of metabolic syndrome.

The effects of metformin on BPH are summarized in Table 5. Although cellular and animal studies support a potential beneficial effect of metformin on BPH, its role in humans requires further confirmation.

4. Prostate cancer

1) Cellular and animal studies

A recent cellular study suggested that hyperglycemia may induce epithelial-mesenchymal transition (EMT) and increase the expression of matrix metalloproteinases and cysteine–cysteine (CC) chemokine ligands in PCa tissues, which are important biomarkers of PCa angiogenesis, invasion, proliferation, inflammation, and metastasis [94]. This provides supportive data for a link between hyperglycemia (or diabetes mellitus) and PCa.

Studies conducted in *in vitro* and in animals demonstrated that metformin inhibits PCa cell proliferation, migration, and progression by activating AMPK and blocking mammalian target of rapamycin (mTOR) complex 1 signaling [84,95], by blocking cell cycle in G_0/G_1 through a decrease of cyclin D1 level [96], by inhibiting the forkhead box M1 transcription factor and thus suppressing EMT [97], by inhibiting androgen receptor [68], by inhibiting tumor-associated inflammatory infiltration [98], through up-regulation of pigment epithelium-derived factor [99], by suppressing the expression of enhancer of zeste homolog 2 (EZH2) via upregulating miR-26a-5p [100], by downregulating the *c-myc* oncogene [101], by inhibiting the IGF-1 pathway and via

many other potential molecular pathways which have been extensively reviewed by other investigators [102–104]. The anti-neoplastic activity of metformin on PCa could be enhanced by the combination use with rapamycin [95], 2-deoxyglucose [105], simvastatin [106,107], doxorubicin [108], an inhibitor of polo-like kinase 1 [109], valproic acid [110], GSK126 (an inhibitor of EZH2) [100], exendin 4 [111], aspirin [112], or solamargine (a major steroidal alkaloid glycoside) [113]. Xie et al [114] demonstrated that metformin in combination with abiraterone (a selective inhibitor of androgen biosynthesis) or enzalutamide (an androgen receptor antagonist) might further enhance apoptosis in LNCaP cells. Metformin may also sensitize PCa cells to radiation in an *in vitro* and *in vivo* study [115].

An early *in vitro* and *in vivo* study suggested that metformin inhibited the early development of prostate intraepithelial neoplasia in Hi-Myc mice through suppressing the oncogene *c-myc* [101]. Metformin has been shown to postpone high-fat diet induced PCa in transgenic adenocarcinoma of the mouse prostate (TRAMP) mice [116]. An *in vivo* study that administered metformin to mice bearing xenografts of human PCa cell line (LNCaP) showed a reduction of tumor growth by 35% to 50% [96]. Metformin also reduced EMT and metastasis of PCa in an *in vitro* and animal study using nude mice [117]. It is interesting that an animal study conducted in immunosuppressed mice suggested that the anti-tumor effect of metformin on PCa growth can be modified by diet. Although metformin reduced PCa growth under low-fat diet, its effect was more prominent if the animals were under high-fat diet [69].

2) Diabetes mellitus and prostate cancer risk

In humans, there is an inverse association between diabetes mellitus (or metabolic syndrome) and PCa [118,119], which has been shown in studies conducted mainly in the white people [120-122]. However, in Taiwan we demonstrated that diabetes patients have a significantly higher incidence of [123] and mortality from [124] PCa. The positive association between diabetes mellitus and PCa can also be shown in several other studies conducted in Asian countries [125].

3) Metformin use and prostate cancer risk

Studies using the Taiwan's National Health Insurance database suggested a lower risk of PCa associated with the use of metformin with estimated HR of 0.467 (95% CI, 0.446–0.488) [126] and 0.69 (95% CI, 0.49–0.96) [127], respectively. This was also observed in a Danish study (adjusted OR, 0.84; 95% CI, 0.74–0.96) [128]. An early meta-analysis that included 14 datasets with 963,991 male subjects estimated a significantly reduced risk of PCa associated with metformin use (OR, 0.91; 95% CI, 0.85–0.97) [129]. However, this protective effect of metformin on PCa was not consistently observed in a recent meta-analysis [130].

PCa is characterized by an activation of the PI3K-AKT-mTOR (phosphatidylinositol-3-kinase [PI3K], protein kinase B [PKB/AKT], and mTOR) pathway [131] and deficiency of PTEN (phosphatase and tensin homolog deleted on chromosome 10), a tumor suppressor gene that inhibits the PI3K-AKT-mTOR pathway, is associated with PCa [132]. Metformin is an AMPK activator and induces PTEN [133]. Therefore, metformin is potentially effective in the inhibition of PCa.

Chronic inflammation resulting from prostatitis, BPH, or other etiologies may promote the development of PCa and is a promoter of metastasis and therapeutic resistance in PCa [78,80,81]. The use of metformin as an anti-inflammatory agent in the management of PCa has also been proposed [103,104].

A retrospective cohort study conducted in the USA by using the Veteran Administration Health Care System showed that use of metformin only increased the risk of PCa (HR, 2.16; 95% CI, 1.846–2.536), but when it was used with statin there was a synergistic effect of risk reduction (HR, 0.31; 95% CI, 0.242–0.406) [134]. Another study conducted in the USA suggested that metformin was positively associated with highly aggressive PCa in blacks (OR, 2.01; 95% CI, 1.05–3.83) but not

in whites (OR, 0.80; 95% CI, 0.34–1.85). On the contrary, another USA study that analyzed the risk of PCa in three different ethnic groups with regards to the use of metformin, metformin plus statin and metformin plus finasteride (a 5 α -reductase inhibitor with anti-androgenic activity) showed that metformin use was associated with a reduced risk in the Hispanics but not in non-Hispanic whites and African Americans. However, when metformin was used with statin or finasteride, a significantly reduced risk could be seen in all ethnic groups and there was a trend of synergistic effects [135]. Another USA study suggested that the association between metformin use and PCa aggressiveness can be modified by race: while black people showed an increased risk of high-aggressive PCa associated with metformin use (OR, 2.01; 95% CI, 1.05–3.83), there was an inverse association in the white people (though not statistically significant, OR, 0.80; 95% CI, 0.34–1.85) [136]. It remains to be explored whether the racial discrepancy in the association between metformin use and PCa risk could be partly explained by the dietary difference as shown in the animal study by Sarmiento-Cabral et al [69]. Therefore, the interaction of metformin with the use of other drugs, diet and race/ethnicity should better be considered in future research.

4) Metformin use as an adjuvant therapy for prostate cancer

Even though a cellular study suggested a favorable outcome when metformin was used in combination with abiraterone or enzalutamide [114], a recent phase 2 pilot clinical trial conducted in Switzerland that recruited a small sample size of 25 men with metastatic castration-resistant PCa and PSA progression did not support any beneficial effect of metformin used on top of abiraterone treatment [137]. It is not known whether the lack of a benefit of metformin in this clinical trial could be because of the inclusion of patients with late stage PCa and the small sample size. The potential usefulness of metformin as an adjuvant therapy for PCa requires more in-depth research. Currently, at least 26 clinical trials evaluating the adjuvant effect of metformin on PCa therapy are being conducted since 2009 [20,84].

5) Metformin use and prognosis of prostate cancer

In patients with PCa, a better prognosis associated

with metformin use was observed in retrospective studies conducted in the USA [138] and Canada [139,140]. However, this could not be supported by an early meta-analysis that showed a non-significant association between metformin use and all-cause mortality in patients with PCa (HR, 0.86; 95% CI, 0.64–1.14) by analyzing 5 datasets with an inclusion of 9,241 patients [129]. Another meta-analysis including 8 retrospective cohort studies and 1 nested-case-control study suggested a marginal reduction in the risk of biochemical recurrence (5 studies; HR, 0.82; 95% CI, 0.67–1.01; $p=0.06$) and a lack of association with metastases (3 studies), all-cause mortality (5 studies) or PCa-specific mortality (4 studies) [141]. However, a later meta-analysis including 9 retrospective cohort studies with 9,186 patients with PCa showed a significant improvement in overall survival (HR, 0.88; 95% CI, 0.86–0.90) associated with metformin use, but a non-significant risk reduction of PCa-specific mortality (HR, 0.76; 95% CI, 0.44–1.31) [142]. A recent pooled analysis of two phase 3 randomized trials

even suggested a worse outcome of biochemical relapse-free survival associated with metformin use (adjusted HR, 2.11; 95% CI, 1.03–4.33) in patients with localized PCa and treated with radiotherapy and androgen deprivation therapy [143].

Although the beneficial effects of metformin on PCa are not conclusive [144], some investigators suggested that metformin may have a future role in the treatment of PCa and its potential molecular mechanisms have been reviewed [102,145]. A combination strategy of metformin and other chemotherapeutic agents for PCa can be more effective [146]. In recent years, BPH and PCa have been shown to be associated with cellular senescence [147]. Because metformin can target senescent cells by preventing the induction of senescence-associated secretory phenotype [148,149], the use of metformin may potentially affect the risk of BPH and PCa *via* a mechanism of protecting cellular senescence.

In summary, controversial findings have been reported with regards to the association between diabetes

Table 6. Summary of metformin's effects on prostate-related health: prostate cancer (PCa)

Studies/comments	Main findings
Cellular study	<ol style="list-style-type: none"> 1. Hyperglycemia induces epithelial-mesenchymal transition [94]. 2. Metformin inhibits PCa cell proliferation, migration, and progression [68,95,97-99]. 3. Metformin sensitizes PCa cells to radiation [115]. 4. Metformin's anti-neoplastic activity can be enhanced by the combination use with rapamycin [95], 2-deoxyglucose [105], simvastatin [106,107], doxorubicin [108], an inhibitor of polo-like kinase 1 [109], an inhibitor of enhancer of zeste homolog 2 [100], valproic acid [110], exendin 4 [111], aspirin [112], or solamargine [113]. 5. Metformin in combination with abiraterone or enzalutamide enhances apoptosis in PCa cell lines [114].
Animal studies	<ol style="list-style-type: none"> 1. Administration of metformin to mice bearing xenografts of human PCa cell line (LNCaP) results in a reduction of tumor growth by 35% to 50% [96]. 2. Metformin postpones high-fat diet induced PCa in transgenic adenocarcinoma of the mouse prostate (TRAMP) mice [116]. 3. Anti-tumor effect of metformin on PCa in immunosuppressed mice is more prominent if the animals are fed a high-fat diet [69]. 4. Metformin attenuates the development of prostate intraepithelial neoplasia by suppressing the oncogen <i>c-myc</i> [101]. 5. Metformin sensitizes PCa cells to radiation [115]. 6. Metformin reduced metastasis of PCa in nude mice [117].
Human studies	<ol style="list-style-type: none"> 1. Metformin use is associated with a lower risk of PCa in patients with type 2 diabetes mellitus [126-128]. 2. Meta-analyses do not consistently conclude with a reduced risk of PCa associated with metformin use. Refer to meta-analyses by Yu et al [129] and Wang et al [130]. 3. The reduced risk of PCa associated with metformin use is especially significant when it is used with statin [134,135] or finasteride [135]. 4. The association between metformin use and PCa aggressiveness can be modified by race [135,136]. 5. Metformin use as an adjuvant therapy for PCa is under investigation, but the prognosis of PCa associated with metformin use is not conclusive. For some meta-analyses, please refer to: [129,141-143,145].
Author's comments	<ol style="list-style-type: none"> 1. Whether metformin may affect the risk of PCa in diabetes patients or affect the prognosis of patients with PCa is not conclusive. 2. Metformin is currently being investigated as an adjuvant therapy for PCa in more than 26 clinical trials [20]. 3. Interested readers may refer to review articles by Wang and Olumi [84], Zaidi et al [102], Hayashi et al [103], Hatano et al [104], and Campi et al [144].

mellitus and PCa, the effects of metformin on PCa prevention and the effects of metformin on PCa aggressiveness and prognosis after the diagnosis and treat-

ment of PCa. It is worthy to mention that the use of metformin as a preventive agent for PCa is a different issue from the use of metformin as a therapeutic agent

Table 7. Potential mechanisms explaining metformin's effects in men's reproductive health and prostate-related health

Effect	Potential mechanisms
Reproductive health	
Erectile dysfunction (ED)	Potential improvement of arteriogenic ED by: <ol style="list-style-type: none"> 1. Restoring the expression of nitric oxide synthase 2. Enhancing endothelium-dependent vasodilatation 3. Attenuating sympathetic nerve activity 4. Lowering blood pressure 5. Reducing risk of ED-related comorbidities 6. Improving insulin resistance and metabolic profiles
Steroidogenesis/spermatogenesis	Results remain inconsistent and more research is required. Potential harms: reduced testicular size, testosterone synthesis and spermatogenesis, by: <ol style="list-style-type: none"> 1. Lactate accumulation 2. Reduced prolactin level (role unknown) 3. Vitamin B12 deficiency (speculative) Potential benefits: metformin is neither genotoxic nor cytotoxic to the testes and may reduce testicular injury, increase testosterone synthesis and improve spermatogenesis, by: <ol style="list-style-type: none"> 1. Up-regulating anti-oxidant enzymes 2. Down-regulating inflammation and apoptosis 3. Restoring gonadotropin and leptin system 4. Improving insulin resistance and metabolic profiles 5. Alleviating blood-testis barrier damage induced by oxidative stress 6. Co-administration of Malaysian propolis or honey may potentiate metformin's benefit
Prostate-related health	
Prostate specific antigen (PSA)	Metformin may reduce PSA levels by inhibiting androgen receptor function
Prostatitis	Not researched but may have potential benefits through metformin's anti-glycemic, anti-microbial and anti-inflammatory properties
Benign prostate hyperplasia (BPH)	Potential benefits by: <ol style="list-style-type: none"> 1. Inhibiting insulin-like growth factor 1 pathway 2. Epigenetic modulation of certain genes 3. Improving insulin resistance and metabolic profiles 4. Targeting cellular senescence
Pancreatic cancer (PCa)	Metformin may prevent the development of PCa and may be useful as an adjuvant therapy for PCa by: <ol style="list-style-type: none"> 1. Attenuate hyperglycemia which may induce epithelial-mesenchymal transition and increase the expression of matrix metalloproteinases and cysteine–cysteine (CC) chemokine ligands in PCa tissues 2. Activating the 5' adenosine monophosphate-activated protein kinase 3. Blocking mammalian target of rapamycin complex 1 signaling 4. Blocking cell cycle in G₀/G₁ through a decrease of cyclin D1 5. Inhibiting the forkhead box M1 transcription factor and thus suppressing epithelial-mesenchymal transition 6. Inhibiting androgen receptor 7. Inhibiting tumor-associated inflammatory infiltration 8. Up-regulating pigment epithelium-derived factor 9. Suppressing the expression of enhancer of zeste homolog 2 10. Downregulating the <i>c-myc</i> oncogene 11. Inhibiting insulin-like growth factor 1 pathway 12. Sensitizing PCa cells to radiation 13. Suppressing inflammation 14. Improving insulin resistance and metabolic profiles 15. Targeting cellular senescence 16. Anti-PCa effect of metformin can be enhanced by concomitant use with other chemotherapeutic drugs

for PCa. Therefore, the preventive effects and the therapeutic effects of metformin on PCa should not be mixed up and be investigated separately. It is possible that metformin may not be effective as a therapeutic agent but it can still play some preventive role. The potential application of metformin in the prevention and treatment of cancers in non-diabetes patients has been reviewed and can also be expected [150].

The effects of metformin on PCa are summarized in Table 6. While cellular and animal studies show a potential role of metformin on the inhibition of PCa development, growth and metastasis, the benefits of metformin on the prevention and treatment of PCa in humans remains controversial and requires more in-depth investigation.

As a summary for the potential roles of metformin on prostate-related health, it is possible that metformin may exert a direct effect on the prostate because it is highly accessible in the prostate, or *via* an indirect effect by correcting the metabolic syndrome. It is noted in the literature that metformin use in humans is associated with a lower level of PSA, but the clinical implications remain to be investigated. Whether metformin may affect the risk of prostatitis has not been studied. Use of metformin may potentially reduce the risk of BPH through the inhibition of the IGF-1 pathway. Metformin may also reduce the risk of PCa and its role in the treatment of PCa is being researched. Although the findings remain inconclusive, more studies are required to identify the subgroups of patients who can be benefited from the use of metformin.

CONCLUSIONS

This narrative review focuses on the effects of metformin on men's reproductive health and prostate-related health. Main findings from updated literature are summarized in Table 1-6 and the potential mechanisms are depicted in Table 7. In summary, metformin may exert potential benefits on arteriogenic ED but its effects on testicular steroidogenesis and spermatogenesis are controversial. While some suggest a protective effect on testicular injury with increased testosterone synthesis and improvement of sperm quality and quantity, others concluded with a harmful effect. With regards to prostate-related health, metformin use in humans is associated with a lower level of PSA, but its clinical implications are not clear. Metformin's ef-

fect on prostatitis has not been researched, but it may potentially reduce prostate infection and inflammation. Metformin may reduce the risk of BPH by inhibiting the IGF-1 pathway or by improving insulin resistance and metabolic syndrome. Because of a potential anti-cancer effect of metformin, the benefits of metformin use on PCa risk, therapy and prognosis are hot topics currently under enthusiastic research. However, its clinical applications remain to be confirmed.

Conflict of Interest

The author has nothing to disclose.

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