Therapeutic effect of metformin in the treatment of endometrial cancer (Review)

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Abstract. The present review aims at reviewing the role of metformin in the treatment of endometrial cancer (EC). According to the literature, excessive estrogen levels and insulin resistance are established risk factors of EC. As a traditional insulin sensitizer and newly discovered anti-cancer agent, metformin directly and indirectly inhibits the development of EC. The direct mechanisms of metformin include inhibition of the LKB1-AMP-activated protein kinase-mTOR, PI3K-Akt and insulin-like growth factor 1-related signaling pathways, which reduces the proliferation and promotes the apoptosis of EC cells. In the indirect mechanism, metformin increases the insulin sensitivity of body tissues and decreases circulating insulin levels. Decreased levels of insulin increase the blood levels of sex hormone binding globulin, which leads to reductions in circulating estrogen and androgens. The aforementioned findings suggest that metformin serves an important role in the treatment of EC. Increased understanding of the mechanism of metformin in EC may provide novel insights into the treatment of this malignancy.

Contents

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1. Introduction

Endometrial cancer (EC) is a malignant gynecological disease that is prevalent in the developed world. It has been estimated that ~63,230 women were diagnosed with EC and 11,350 women succumbed to this malignancy in 2018 in the United States alone (1). The etiology of EC has not yet been clearly elucidated. Traditionally, the 'unopposed estrogen' hypothesis has been considered to explain the carcinogenesis of EC (2). According to this theory, without sufficient progestins to oppose them, excessive endogenous and/or exogenous estrogens stimulate proliferation and inhibit apoptosis of the endometrium. This process has been considered to contribute to the pathogenesis of EC. Data from numerous studies suggest that insulin resistance is associated with a high risk of EC (3). Our previous study revealed that elevated insulin levels, which is associated with insulin resistance, is an independent risk factor for EC in premenopausal women (4). Another study has reported that insulin resistance-induced hyperinsulinemia independently increases the risk of EC in postmenopausal women (5). Furthermore, another of our previous studies demonstrated that hyperinsulinemia is positively associated with lymph node metastasis in patients with EC and indicates a poor prognosis (6).

At present, surgery is the most effective treatment option for this malignant disease. According to the National Comprehensive Cancer Network guidelines, a surgical procedure including total hysterectomy and bilateral accessory resection, pelvic lymph node dissection and para-aortic lymph node dissection is the most effective treatment method for EC (7). However, this surgical procedure leads to a permanent loss of fertility in patients with EC. According to a previous report (8), ~25% of patients with EC are premenopausal, and 3~5% of these patients are <40 years old and want to retain fertility. Among the latter patients, 70-88% have not completed childbearing, and most of them exhibit early-stage highly differentiated endometrioid endometrial carcinoma with a good prognosis. Additionally, some patients cannot undergo

surgery due to serious complications. Currently, progesterone is widely used in the conservative treatment of EC. However, >30% of patients are insensitive or resistant to progesterone treatment (9). Furthermore, side effects, including thrombosis, liver damage, weight gain and progesterone resistance, greatly limit the application of this agent (10).

Metformin is a well-known first-line agent for the treatment of type 2 diabetes, which inhibits hepatic glucose output and intestinal glucose absorption, and promotes the uptake of glucose by skeletal muscle to alleviate insulin resistance. Metformin has also been suggested to be a potential anticancer agent (11). Studies have reported that metformin inhibits the proliferation of a variety of tumor cells, including gastric cancer, pancreatic cancer, medullary thyroid carcinoma and EC cells, in a dose-dependent manner (12-15). The mechanism of this inhibitory effect has been suggested to be associated with cell cycle arrest and the promotion of apoptosis (16). Our previous study revealed that the combined application of metformin and progestins synergistically inhibits the proliferation of EC cells, and suggested that downregulation of the expression levels of cyclin D1 and cyclin E may be an underlying mechanism of this synergistic inhibitory effect (17). Based on the aforementioned results, it may be concluded that metformin is a promising therapeutic option for EC. The anticancer effect of metformin in EC appears to be mediated via direct and indirect mechanisms, which are described in the following sections of this review. Relevant articles and studies were identified using Medline with the following key words alone or in combination: 'Endometrial cancer', 'metformin', 'treatment', 'signaling pathway', 'insulin resistance', 'insulin', 'inflammatory factor' and 'adipokines'.

2. Metformin indirectly inhibits the development of EC

Association between insulin resistance and EC. Insulin resistance is characterized as a reduction in the insulin sensitivity of body tissues during metabolic activity, leading to an increase in circulating insulin levels (18). Insulin resistance is known to reduce the insulin-mediated utilization of glucose by the body. This has been suggested to be one of the most important mechanisms of the pathogenesis of diabetes (19). Furthermore, it has been noted that conditions other than diabetes that are closely associated with insulin resistance, namely hypertension, coronary heart disease and hyperlipidemia, also serve important roles in the pathogenesis of certain malignant diseases such as EC, breast cancer and colon cancer (20).

In cases of insulin resistance, particularly in the early stages, circulating insulin levels may be higher than normal (21). Insulin, which is produced and secreted by pancreatic β cells, regulates glucose homeostasis by regulating hepatic glucose production and the uptake of glucose by fat and muscle tissue (22). The role insulin serves in tissues is mediated via the insulin receptor, which comprises insulin receptor α (IRα) and IRβ subtypes. IRα has a ligand-binding domain that is activated by insulin-induced autophosphorylation. Total insulin receptor and IRα expression levels in EC tissues have been identified to be higher than those in normal endometrial tissues *in vivo*, whereas *in vitro*, the overexpression of IRα has been shown to be positively associated with EC cell proliferation (23). This suggests that the activation of insulin signaling is likely to be closely associated with the carcinogenesis of EC. Furthermore, insulin has been suggested to act as a direct mitogenic promoter in the malignant transformation of the endometrium (24). Additionally, it has been reported that excessive insulin inhibits the production of sex hormone binding globulin (SHBG), leading to increased levels of free estrogens and androgens (25). Subsequently, excessive estrogens promote the carcinogenesis of EC according to the 'unopposed estrogen' hypothesis, while excessive androgens provide additional substrate for aromatase-catalyzed biotransformation to estrogen in adipose tissue, resulting in increased circulating levels of estrogen that stimulate the pathogenesis of EC.

There is evidence to suggest that diseases associated with insulin resistance are also risk factors of EC. Body mass index (BMI) is an effective indicator of obesity. It has been reported that patients with a higher BMI usually have a higher risk of EC (26). A clinical study found that elevated BMI value means increased EC risk (27). Furthermore, in another study, the waist-to-hip ratio of patients with EC was shown to be markedly higher than that of control patients with benign endometrial lesions (28), which is consistent with previous findings that upper body obesity is closely associated with EC risk (29). Obese patients often have excessive adipose tissue in which estrogen biosynthesis can occur. Additionally, greater amounts of adipose tissue are usually associated with higher levels of adipokines and inflammatory factors, and these have been suggested to serve an important role in the carcinogenesis of EC (30,31). Type 2 diabetes is another risk factor for both insulin resistance and EC. Increased serum insulin levels have been reported to increase the risk of EC in the early stage of diabetes in a dose-dependent manner (32), and hyperinsulinemia is considered to be an independent risk factor for EC (33). In addition to increasing the incidence of EC, type 2 diabetes also increases the risk of death in patients with EC (34). Furthermore, type 2 diabetes combined with obesity markedly increases EC risk (35). The fasting insulin levels and insulin resistance index values of patients with EC have been shown to be higher than those of controls with benign endometrial lesions (28). Insulin resistance is not only a disease, but also a key pathophysiological process in obesity, diabetes, hypertension and metabolic syndrome. Strategies to promote weight loss, including dietary adjustments and regular physical activity, have been suggested to effectively decrease the risk of insulin resistance as well as that of EC (36).

Metformin inhibits the development of EC by ameliorating insulin resistance. Our previous review suggested that insulin resistance serves a central role in the pathogenesis of EC (3). As an effective insulin sensitizer, metformin greatly improves the utilization of insulin by body tissues to ameliorate insulin resistance. As a result, circulating insulin levels are decreased, which decreases the risk of EC induced by excessive insulin (37). Additionally, the downregulation of circulating insulin levels is considered helpful in the control of body weight, and reductions in body weight have been suggested to inhibit the carcinogenesis of EC (38). This may be at least partly explained by downregulated levels of adipokines and inflammatory factors. A clinical trial has demonstrated that

metformin delays the development of obesity by improving the resistance status of leptin and insulin growth factor-1 decreasing the levels of insulin, which inhibits the development of EC (39). Additionally, metformin has been reported to increase adiponectin gene expression levels in obese patients, promote the secretion of adiponectin from adipose tissue and thereby induce the apoptosis of EC cells (40). Furthermore, the loss of adipose tissue due to body weight reduction results in less tissue being available for aromatase-catalyzed estrogen biosynthesis. Overall, it may be concluded that metformin indirectly inhibits the development of EC by ameliorating insulin resistance.

3. Metformin directly inhibits the development of EC

Metformin has been reported to inhibit the proliferation, migration and invasion of EC cells, and to promote tumor cell apoptosis. However, the specific mechanism remains unclear. Current data suggest that metformin may inhibit the development of EC via a number of pathways described hereinafter.

Hepatic kinase B1 (LKB1)-AMP-activated protein kinase (AMPK)-mTOR signaling pathway. Metformin has been reported to increase glucose uptake by activating the AMPK signaling pathway (41). AMPK is a heterotrimeric serine/threonine protein kinase complex composed of a catalytic α subunit and regulatory β and γ subunits. AMPK has been suggested to be responsible for the regulation of energy metabolism. It is activated by the cellular stress induced by decreased cellular energy levels and an increased AMP/ATP ratio (42). Once activated, AMPK restores cellular energy levels by stimulating catabolic signaling pathways, including glucose uptake, glycolysis and fatty acid oxidation, and inhibiting ATP-depleting processes, such as fatty acid, cholesterol and protein synthesis (43). LKB1, also known as serine/threonine kinase 11, is an upstream kinase of AMPK that is generally considered to be a tumor suppressor gene. Biochemical and genetic analyses have revealed that under energy stress, LKB1 activates AMPK by phosphorylating AMPK (44). Loss of LKB1 gene expression has been identified in ~65% of patients with EC (45). LKB1 expression is inversely associated with tumor grade and stage; the inactivation or downregulation of LKB1 promotes the progression of EC and its loss promotes a highly invasive phenotype. As a tumor suppressor gene, LKB1 may inhibit the occurrence and development of EC via the LKB1-AMPK-mTOR signaling pathway (46).

Metformin enters cancer cells via the organic cationic transporter, and inhibits the activity of the respiratory transporter complex, thereby reducing ATP production. The reduction in ATP level activates the tumor suppressor gene LKB1, which then phosphorylates AMP (46). AMPK regulates several signaling pathways and controls cell proliferation, primarily via inhibition of the mTOR signaling pathway. The available data suggest that the antiproliferative effect of metformin on cancer cells is likely to be mediated via the LKB1-AMPK signaling pathway. For example, in a study of breast cancer cells, metformin activated AMPK by phosphorylating LKB1, and thus inhibited tuberous sclerosis complex 2 phosphorylation and mTOR pathway activation, resulting in the proliferation and apoptosis of the cells being decreased and increased, respectively (47). Also, the results of an *in vitro* study using ECC-1 and Ishikawa cells demonstrated that metformin reduced cell proliferation and increased AMPK activation in a dose-dependent manner, and indicated that the mTOR signaling pathway inhibition contributed to these effects (48). Metformin has been found to be functionally similar to an mTOR inhibitor, and the PTEN signaling pathway, which is tightly associated with the carcinogenesis of EC, may also be a target of metformin (49). Experiments in mice demonstrated a 50% reduction in the weight of EC xenografts following treatment with metformin, mediated via inhibition of the LKB1-AMPK-mTOR signaling pathway (50). Metformin has also been revealed to suppress the development of EC xenografts and ameliorate metabolism disorders in obese mice, with the LKB1-AMPK-mTOR signaling pathway being suggested to be partly responsible for the therapeutic effects (51).

PI3K-Akt signaling pathway. PI3K is a cytoplasmic enzyme that is an important member of the phospholipase family, promoting cell proliferation (52). It has both lipid and protein kinase activities. According to the composition of the lipid kinase, PI3K is divided into three subclasses: I, II and III. Class I PI3K is a heterodimer consisting of a catalytic subunit and a regulatory subunit. It is divided into two subclasses: IA (composed by PIK3 CA, PIK3 CB and PIK3 CD) and IB (encoded by PIK3 CG). PIK3 CA is more susceptible to mutation than PIK3 CB (53), and has been reported to serve an important role in the development of several malignant diseases (54). Class I PI3K phosphorylates phosphatidylinositol 4,5 diphosphate (PIP2) to form 3,4,5-trisphosphate phosphatidylinositol (PIP3). Subsequently, PIP3 acts as a second intracellular messenger that is involved in several molecular biological events such as the promotion of cell proliferation and the inhibition of apoptosis (55). PTEN is a phosphatase gene homologous to tensin, which is located on human chromosome 10 q23 and acts as a tumor suppressor gene. PTEN dephosphorylates PIP3 to form PIP2, which serves a negative regulatory role in the downstream signaling pathway of PI3K (56). The activation of PI3K and functional inactivation of PTEN by mutation have been identified in several human malignant tumors, suggesting that PI3K is associated with tumor pathogenesis (57). Protein kinase B, also known as Akt, is a downstream signaling molecule of PI3K that is activated by the phosphorylation of phosphatidylinositol family members on the cell membrane. Subsequently, activated Akt phosphorylates the Ser196 of cysteinyl aspartate specific proteinase (caspase)-3 and caspase-9, thereby inhibiting apoptosis. The lipid phosphatase activity of PTEN has a tumor-suppressing effect mediated via specific dephosphorylation of the phosphatidylinositol D3 ring, which antagonizes phosphorylation of the PI3K substrate and negatively regulates the PIK3-Akt signal transduction pathway (58).

PIK3CA mutation and PTEN deletion are common molecular biological events in EC (59). Clinical data have revealed that the upregulation of PI3K expression and downregulation of PTEN expression frequently occur in patients with EC (60). *In vitro* data have demonstrated that the PI3K-Akt signaling pathway contributes to the carcinogenesis of EC (61). A study

of patients with EC observed that PTEN expression is negatively associated with myometrial invasion depth, indicating that PTEN may play an important role of in the development of EC and is potentially a prognostic indicator of EC (62). It has been reported that metformin inhibits Akt expression and stimulates PTEN and IP3 expression via inhibition of the PI3K-Akt signaling pathway (63). This is considered to be an important mechanism via which metformin inhibits the development of EC; both *in vitro* and *in vivo* evidence suggest that inhibition of the PI3K-Akt signaling pathway is a key mechanism via which metformin suppresses the carcinogenesis and metastasis of EC (64). A study demonstrated that metformin inhibits the proliferation and colony formation of EC cells in a time- and dose-dependent manner, and suggested that the PI3K-Akt signaling pathway is partly responsible for this inhibitory effect (65). Furthermore, endometrial hyperplasia has been shown to be reversed by metformin management, with suppression of the PI3K-Akt-mTOR signaling pathway appearing to serve a key role in this inhibitory effect (37). Additionally, it has been suggested that metformin management is an effective preventative strategy for EC (63).

Insulin-like growth factor 1 (IGF-1)-associated signaling pathway. IGF-1 is an important member of the IGF family, promoting cell proliferation (66). It is a 70-amino-acid peptide that is synthesized by the liver and is structurally similar to insulin. IGF-1 promotes cell division and has anti-apoptotic effects; it promotes tissue cell proliferation, inhibits apoptosis and regulates tumor pathogenesis via autocrine and paracrine mechanisms (67). As a regulator of cell proliferation, IGF-1 accelerates the transport of amino acids and glucose into cells, thereby increasing protein synthesis and reducing protein degradation, and exerts strong mitogenic effects (68). When IGF-1 binds to the IGF-1 receptor (IGF-1R), PI3K-Akt is activated and the IGF-1-PI3K-Akt signaling pathway is stimulated. Furthermore, IGF-1 also activates the mitogen-activated protein kinase-ERK signaling pathway, thereby inducing tumor cell transcription (69). The overexpression of IGF-binding protein-1 (IGFBP-1) has been shown to inhibit the IGF-1 signaling pathway and reduce the uterine response to IGF-1 (23). In the normal endometrium, IGF-1 expression is induced by estrogen; however, IGFBP-1 suppresses IGF-1 expression and its activity (70). In addition, insulin increases the biological activity of IGF-1 by downregulating IGFBP-1 expression in the endometrium (71). It has been reported that EC cells synthesize and secrete IGF-1, which regulates cell proliferation and differentiation via autocrine and paracrine mechanisms, resulting in continuous proliferation of the cells (72).

As an insulin sensitizer, metformin decreases circulating insulin levels and thereby inhibits the IGF-1-induced phosphorylation of Akt (39). Metformin has been found to not only block the regulatory effect of feedback from the IGF-1R signaling pathway, but also to induce tumor cell apoptosis when combined with IGF-1R inhibitors (73). Clinical data suggest that a regular dose (500 mg/time, 3 times per day) of metformin effectively reduces elevated IGF-1 levels in the circulation of patients with EC and decreases IGF-1 expression in cancer tissues (74). In an *in vitro* study, metformin delayed and prevented the IGF-1R feedback-induced proliferation of EC cells, with high concentrations of metformin markedly promoting the apoptosis of EC cells (67). In an *in vivo* study, the intraperitoneal injection of metformin markedly reduced the circulating IGF-1 levels in mice and strongly inhibited the development of xenograft tumors (75). In addition to suppressing the proliferation-promoting effect of IGF-1 and IGF-2, metformin has also been shown to increase progesterone receptor expression, which appears to be beneficial in the treatment of EC (72).

Apoptosis-stimulating effect. Caspases are a group of cytoplasmic proteases with similar structures. They are responsible for selectively cleaving certain proteins, which leads to apoptosis. Genetic polymorphisms in caspase genes may affect the risk of cancer by altering the expression levels and function of these genes (76). Caspase-3 and -7 have been identified as key performers of cell apoptosis and serve a central role in the execution phase of apoptosis (77). Caspase-8 is required for death receptor-mediated apoptosis, whereas caspase-9 is required for mitochondria-mediated apoptosis. The activation of caspase-8 and -9 induces the subsequent activation of other cysteine proteases and promotes cell apoptosis (78). Inactivating mutations of the caspase gene have been suggested to be associated with the pathogenesis of certain human solid cancers, including EC (76). Metformin activates caspase-8/9 by promoting the electron transport chain and membrane permeability, and the activation of caspase 8/9 leads to the subsequent activation of other caspase enzymes, thereby reducing cell proliferation and promoting apoptosis (79,80). The stimulating effect of metformin on members of the caspase family is dose-dependent (81).

Autophagy refers to the process of cell degradation induced by exogenous stimuli, in which degradation products, such as those derived from the endoplasmic reticulum and Golgi apparatus are recovered and transported to the lysosome for catabolism in order to recycle energy and maintain the stability of the intracellular environment (82). As a signaling pathway for cell survival, autophagy suppresses the cellular stress response and genomic damage by eliminating abnormally folded proteins and organelles, such as mitochondria and lysosomes, from tumor cells, thereby suppressing the occurrence of cancer. The expression levels of Beclin 1, an autophagy-associated gene, have been shown to be positively associated with the tumor grade and degree of myometrial infiltration in EC (83). High Beclin expression is associated with high expression of hypoxia inducible factor 1α. Increased autophagy appears to aid tumor survival in a hypoxic microenvironment (84). Microtubule-associated protein 1A/1B-light chain 3 (LC3) expression may be considered a marker of excessive autophagy in EC (85). It has been reported that metformin induces autophagy in colon cancer, melanoma and Ishikawa EC cells (86). Upregulation of the expression levels of autophagy-associated genes, including LC3 and Beclin 1, is considered to be a mechanism via which metformin promotes cell autophagy (87). Furthermore, the knockdown of Beclin 1 expression or inhibition of caspase-3/7 has been shown to inhibit metformin-induced cell autophagy and promote cell proliferation (88). Therefore, metformin promoted autophagy, induced apoptosis and suppressed cell survival in ovarian cancer cells (89).

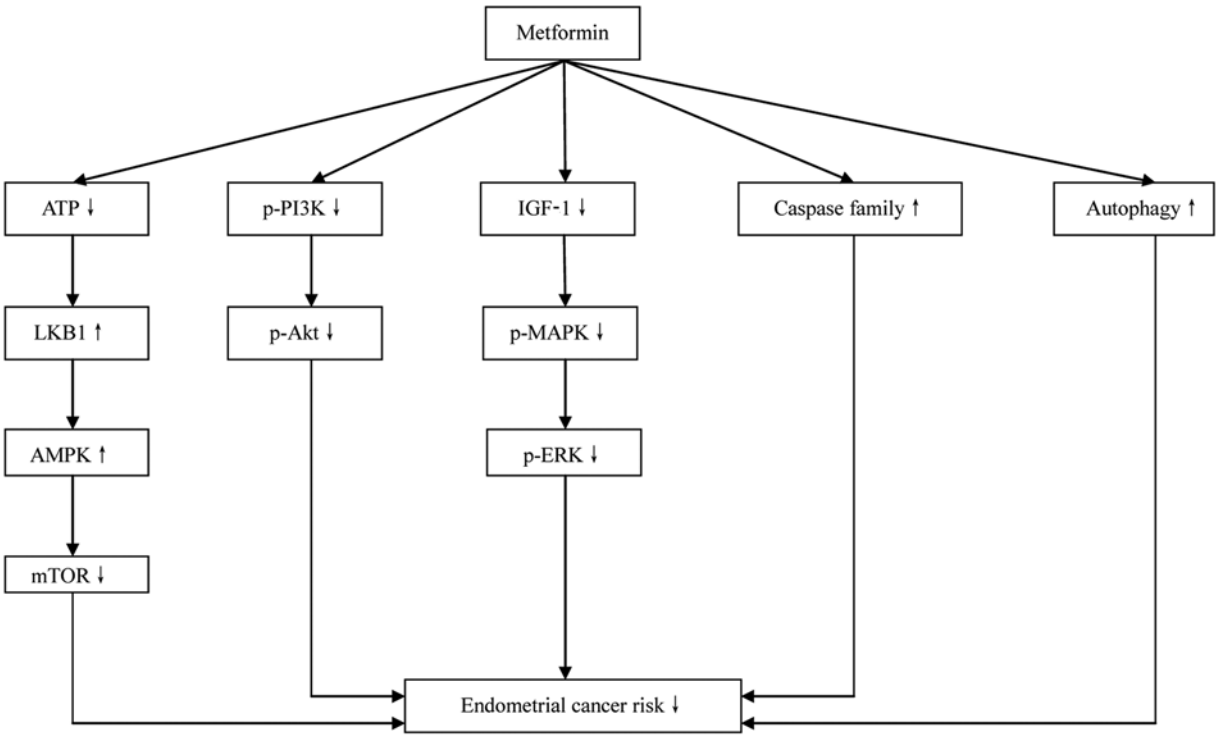

Figure 1. Mechanisms by which metformin directly inhibits the development of endometrial cancer. LKB1, hepatic kinase B1; AMPK, AMP-activated protein kinase; p, phospho; IGF-1, insulin-like growth factor 1; MAPK, mitogen-activated protein kinase.

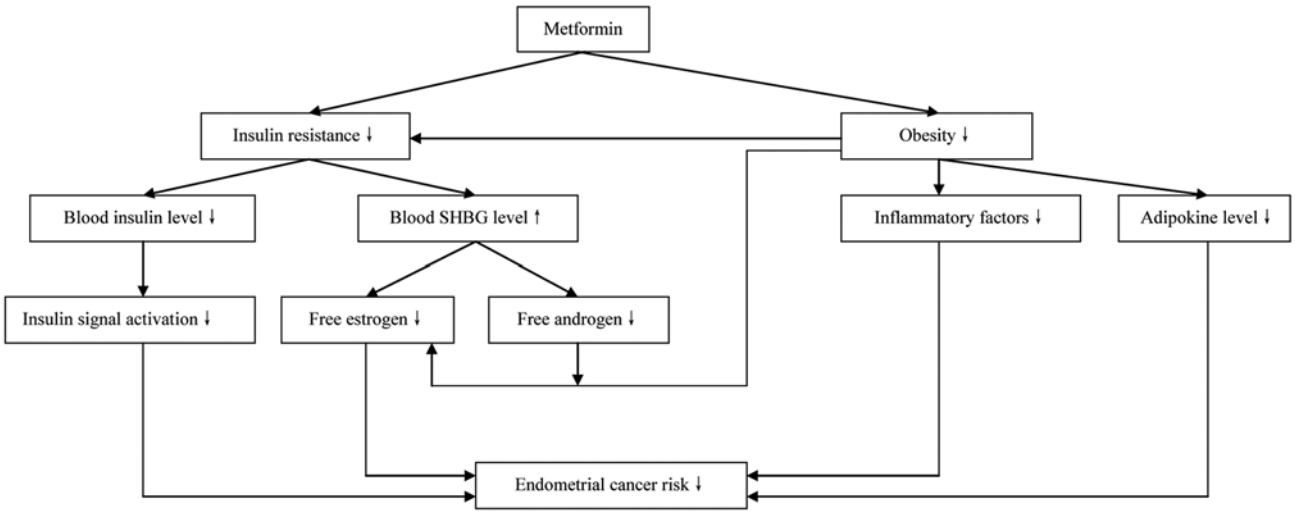

Figure 2. Mechanisms by which metformin indirectly inhibits the development of endometrial cancer. SHGB, sex hormone globulin binding.

4. Clinical studies of the therapeutic effect of metformin on EC

Unfortunately, clinical data regarding the effect of metformin in EC are limited. The results provided by different studies are conflicting. One study revealed that the use of metformin in women with diabetes is associated with a lower overall risk of EC (90). However, another study indicated that metformin does not significantly affect the risk of EC (91). Although some studies have investigated the association between metformin use and the survival of patients with EC, whether the use of metformin is associated with improved clinical outcomes in patients with EC remains unclear. In one study, it was demonstrated that patients who did not receive metformin had a 2.3-fold increased risk of mortality compared with patients receiving metformin after adjustments for age, stage, grade, histology and adjuvant treatment (92). However, another study revealed that the overall survival of patients with EC who had or had not received metformin treatment was similar after adjusting for confounding covariates (93). Endometrial hyperplasia is an important precancerous condition of EC. Clinically, progesterone agents and levonorgestrel intrauterine devices have been widely used in the treatment of endometrial hyperplasia. However, the side effects and continued

risk of recurrence associated with these therapeutic methods have been reported in several studies (94). In a small-scale clinical study, metformin was used in combination with medroxyprogesterone acetate in the treatment of endometrial hyperplasia and EC limited to the endometrium. After 36 weeks, 29 out of 36 patients achieved a complete response. It was noted that 6 of 36 patients suffered diarrhea and nausea when the daily dose of metformin was 2,250 mg (95). However, it was not confirmed whether there were any other potential causes of these side effects. As a novel medication in the treatment of endometrial hyperplasia and EC, the effect of metformin requires further investigation.

5. Conclusion

In summary, *in vivo* and *in vitro* evidence suggests that metformin serves an important role in the treatment of EC. Overall, metformin directly (Fig. 1) and indirectly (Fig. 2) inhibits the development of EC. The direct mechanism involves inhibition of the LKB1-AMPK-mTOR, PI3K-Akt signaling pathways. Furthermore, IGF-1-associated signaling pathways are inhibited by metformin. Metformin also inhibits the development of EC through its effect on caspase family members and the stimulation of autophagy. Insulin resistance is an established EC risk factor that is important in the indirect mechanism of metformin. The risk factors for insulin resistance also promote the carcinogenesis of EC. In the state of insulin resistance, decreased insulin sensitivity of the body tissues results in elevated levels of circulating insulin. Subsequently, excessive insulin downregulates SHBG levels and upregulates estrogen and androgen levels in the blood, which stimulates the pathogenesis of EC. As an insulin sensitizer, metformin effectively promotes the utilization of insulin by the body tissues, which reduces circulating insulin levels and thereby decreases the insulin-associated risk of EC development.

In conclusion, although the experimental data support the therapeutic effect of metformin in EC, the detailed mechanisms of the therapeutic effect of metformin remain unclear. Furthermore, the clinical applicability of metformin alone or in combination with other medications remains uncertain. These topics warrant further investigation in the future.

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JH and YY designed and arranged the manuscript. NM, TX and MG wrote the article. MD, QT, LH, GW, ZL and WW found and analyzed the references in Medline, participated in writing the current paper and gave final approval of the version to be published. NM and TX revised the paper. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

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Competing interests

The authors declare that they have no competing interests.

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