Metformin is probably a new option in the treatment of endometrial cancer

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Endometrial cancer (EC) is a common gynecological malignancy in western countries. Besides excessive estrogen exposure, many other risk factors have been observed, such as obesity, type II diabetes mellitus and polycystic ovary syndrome. To date, surgery remains to be the major treatment for endometrial cancer. However, surgical treatment seems to be unsuitable to some patients. Moreover, none effective method has been provided to prevent this malignancy. On the other hand, insulin resistance was suggested to play an important role in the development of endometrial cancer according to previous studies. Metformin is a common insulin-sensitizing agent used in the treatment of type II diabetes mellitus. The antitumor effects of this old drug have been increasingly reported in recent years. We propose that metformin will block the development of EC through different ways. Therefore, studying the mechanisms of metformin will provide us novel insights on both preventative and therapeutic medical strategies of endometrial cancer.

Keywords: Endometrial Cancer; Metformin; Prevention; Treatment

Introduction

Endometrial cancer (EC) is the most common gynecological malignancy of female reproductive tract in western countries. Unfortunately, the etiology of EC has not been clearly understood. Up to date, medical treatment for EC is primarily surgery, including total abdominal hysterectomy and bilateral salpingo-oophorectomy, with additional lymph node dissection in high risk cases1-3. However, these surgery tools added potential threat to about 20% of the EC patients who are premenopausal women wishing to maintain fertility2. In addition, there are also some EC patients for whom surgical treatment appears to be unsuitable because of morbidly obese and some other serious complications. Besides surgery, much work has been done in understanding the mechanism of development of EC. Currently, the most prevailing hypothesis is “unopposed estrogen”4, 5. However, increasing evidence indicates “unopposed estrogen” is probably only a part of the whole story. Obesity6, type II diabetes mellitus7 and polycystic ovary syndrome (PCOS)8 have been suggested as potential risk factors of EC. Furthermore, insulin resistance which is considered to play an important role in the development of EC9 is indicated as the common pathological character of these diseases.
Metformin is a widely used insulin-sensitizing agent. It is used in the treatment of type II diabetes mellitus by inhibiting the hepatic glucose and lipid synthesis as well as increasing muscle glucose uptake. Moreover, the antitumor effects of metformin also attracted the researchers’ attention in recent years [10]. Based on the information above, it is possible that metformin is a new option to prevent and cure EC.

**Hypothesis**

Based on the insulin-sensitizing and antitumor effects of metformin and the pathological features of EC, we propose that metformin is a potential new option to prevent and cure EC.

**Evaluation of Hypothesis**

**Effects of Metformin on Blood Sex Hormone Level**

Due to insulin resistance or other pathological states, blood insulin concentration will increase. Then, blood sex hormone levels are probably changed subsequently. Sex hormone binding globulin (SHBG) is a pivotal factor regulating the circulation sex hormone concentration by tightly binding to the sex hormones. However, the production of this regulator was indicated to be inhibited by insulin [11]. As a result, free sex hormones level is elevated with high insulin concentration. Excessive free estrogens then promote the development of EC according to “unopposed estrogen” theory. Excessive androgens will supply more substrate for peripheral estrogen conversion. In postmenopausal women, peripheral estrogen conversion serves as their primary source of estrogens. Accompanied by lacking of progestin, excessive estrogen converted from androgens will urge the development of EC. In premenopausal women, excessive androgens can induce anovulation. Without sufficient progestin to counterbalance the tumorigenic effects of estrogens, the development of EC seemed to be promoted.

Metformin is a first line insulin-sensitizing drug used to cure type II diabetes mellitus. It can down regulate the circulating insulin and glucose levels. This appears to make the subjects avoid excessive insulin exposure so as to avoid excessive estrogen and androgen exposure. This is critical for EC patients and subjects who are currently facing EC risk factors, since EC is considered as an endocrine related cancer.

**Effects of Metformin on Signaling Pathways Related to EC**

Blood insulin level is found increased under some pathological states, such as insulin resistance. After binding to its receptor, insulin activate two important signaling pathways, phosphatidylinositol 3-kinase (PI3K)/Akt and Ras/mitogen-activated protein kinase (MAPK). It was reported that activation of either of these two signaling pathways is very critical in the development of EC [12]. Since metformin has the ability to downregulate the blood insulin level, less insulin can be used to activate these two signaling pathways. Although these two signaling pathways maybe not the only promoters of the development of EC, effects of metformin on blood insulin level probably at least partly block the development of this malignancy.

It is widely known that metformin can activate LKB1/AMP-activated protein kinase (AMPK) pathway [13]. Tuberous sclerosis complex-2 (TSC-2) then can be phosphorylated by AMPK which results in inhibition of mammalian target of rapamycin (mTOR) pathway [14]. AMPK was also reported to inactivate mTOR by phosphorylating co-signaling molecules which bind to mTOR [15]. As a result, the survival and proliferation promoting effects of mTOR signaling pathway are inhibited. In EC, inactivation of LKB1 was suggested to play an important role in the development of this malignancy [16]. An investigation showed that over activation of mTOR is common in EC tissues and some EC cell lines, meanwhile the percentage of loss of TSC2 and LKB1 in EC tissue samples is 13% and 21% [17]. Till now, the relationship between metformin and EC was seldom investigated. Breast cancer is a malignant disease which shares similar risk factors, such as excessive estrogen exposure and insulin resistance, with EC. Metformin induced AMPK activation was reported to lead to reduction of mTOR activation [18, 19] and translation initiation [19] in breast cancer cells. Considering the similar pathological features of EC and breast cancer, we propose that effects of metformin on the LKB1/AMPK signaling pathway can also serve the treatment of EC like it dose in the treatment of breast cancer.

Signaling transduction is responsible for plenty of cellular events. As is mentioned above, PI3K/Akt, Ras/MAPK and LKB1/AMPK signaling pathways are showed to play important roles in the development of EC. Blocking these signaling pathways appears to at least partly benefit the patients.

**Effects of Metformin on the Synthesis of Aromatase**

In addition, metformin was reported to inhibit the expression of aromatase in human breast adipose stromal cells, activation of AMPK was reported to be responsible for this inhibitory effect [20]. Since aromatase was considered to be associated with the peripheral conversion of estrogen [21], this observation seems to be also important for EC patient.
Investigations In the Future

First, we should further investigate the mechanism of the effects of metformin on EC. We should make it clear whether there are some new signaling pathways involved in this process. Secondly, animal xenograft model should be employed to examine the effects of metformin on EC in vivo. And more importantly, safety of the application of metformin should further examined in different dose so as to get the most appropriate dose. Third, large scale multi-center prospective studies should be applied to further evaluate this agent.

Conclusion

Metformin has been applied in the treatment of type II diabetes mellitus for a long time. However, the antitumor effects of metformin have only been observed in recent years. Information about the relationship between metformin and EC is very limited. Only one study in vitro [22] and two small case reports [23, 24] can be found. However, these two clinical case reports were too small in scale and no controls were included. A large number of studies in vitro and in vivo are needed in the future to help us understand the mechanism of the effects of metformin on EC. Although very little study has been done on the application of metformin in the treatment of EC, the application of this old drug in the medical treatment of breast cancer has been well studied. A review published in 2010 suggested that metformin is a potential promising agent in the treatment of breast cancer after analyzing a large number of researches [25]. Although the dose of metformin used in most studies are much higher than the standard dose in clinical practice, the application of this drug seems to be safe. A study in vivo showed that the levels of metformin in tissues are much higher than that in blood [26]. Another research found that there is no significant difference between the glucose levels of the control animals and the animals received metformin treatment [27].

As we all know, the development of any cancer is a multi-step and multi-factor process. No single risk factor or signal pathway can promote the pathogenesis of any kind of cancer. Metformin maybe only partly block the development of some types of cancers, such as breast cancer, a malignant disease which shares some common pathological features with EC. Based on the information of the present article, we propose that effects of metformin on blood sex hormone concentrations, signaling pathways related to EC and aromatase production can at least partly benefit the EC patients and the women who are currently facing EC risk. And large scale clinical studies in the future will help us further evaluate this drug.

Conflicting interests

The authors have declared that no conflict of interests exist.

References


