Chapter

Metformin in Health Issues and Reproductive System

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Abstract

Metformin is one of oldest drug in reproductive medicine era; but most of times it is equal to polycystic ovary (PCO) syndrome especially obese patients. If it is still valuable or not, could have another health benefit or new fertility roles, and could be effective as well in male reproductive system will be discussed. According to increased rate of metabolic disorders and cardiovascular problems and cancers, there are several investigations on this old used drug. Those studies had been magnified its role as "the aspirin of current century," which might have a promising role in longevity of the life. So, the chapter will be interesting.

Keywords: metformin, reproductive, health, fertility, metabolic

1. Introduction

Metformin is a component of many herbal therapeutic substances, which has been known since 1500 BCE in Egyptian medicine [1]. In Europe, a herbal remedy was used for ameliorating polyuria and polydipsia; from the Middle Ages, its name was *Galega officinalis* (or the French lilac) [2]. However, just in the early 1900s, the effective element "guanidine" was extracted [3].

Everybody knows that the incidence and prevalence of diabetes mellitus (DM) is increasing constantly. Diabetes is one of the most common noncommunicable diseases and is considered as one of the top five universal causes of precocious death in both developed and non-developed countries. So the immense numbers of studies about metformin, which is the most prevalent and popular remedy for it, could be predictable. As a result, it is no wonder that there is a scanty paper about other worthful aspects of metformin.

Metformin has been called "the aspirin of the twenty-first century [4]." This old-fashioned drug was famous only as antidiabetic drug until recent years. So, what makes this drug so hear saying and impressive for life longevity [5], prevention from cancers [6] and useful in patients with chronic kidney disease, congestive heart failure or chronic liver disease [7]. At the present time, evidence suggests that metformin's wide-spectrum advantages are mediated by at least two relevant pathways: first, by inhibition of intracellular metabolic activity of mitochondria and second, the cellular nutrition-sensing system mediated by mTOR [4]. ("The mammalian target of rapamycin" is one kind of the kinase family that mediates metabolism and cell growth as a reaction to growth factors, nutrients, and stress [8].)

In this chapter we are going to talk about three different fields of metformin action in detail.

2. Health issues

In accordance with aging, there are some significant changes in the body and elevation in prevalence of some specific disease and abnormality [9].

- Endocrine system: type 2 diabetes, thyroid disease, osteoporosis, and orthostatic hypotension
- Cardiovascular: hearth failure, hypertension, and CVD
- Neurological: delirium, cognitive impairment, and dementia
- Optical: macular degeneration, cataract, and presbyopia
- Muscular: impaired mobility, muscular strength, and sarcopenia
- Auditory: presbycusis and conductive hearing loss
- Skeletal: osteoporosis, kyphosis, and scoliosis
- Gastrointestinal: dysphagia, constipation, and malabsorption
- Renal: chronic kidney disease
- Immune: increased risk of infections
- Dermal: dryness and lower elasticity and pressure ulcer

The life span has been regulated by pharmacologic, genetic, and dietary interferences in several sample systems. The most considerable mechanism in aging phenomenon is DNA damage; the endogenous, potent factors are reactive oxygen species (ROS), alkylation, and hydrolysis [10]. Thus, most studies in this subject are focusing on it.

Through the metformin role in aging, it leads to decreased insulin levels, inhibition of mTOR, decreased IGF-1 signaling, endogenous production of reactive oxygen species, inhibition of mitochondrial complex 1, activation of AMP-activated protein kinase (AMPK), and reduction in DNA damage.

Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) is a protein complex that governs transcription of DNA. Metformin inhibits NF-kB, a key point in inflammatory process [11]. Also, by lowering the reactive oxygen species and improving the endothelial function [12], reduction in coronary heart diseases and cerebrovascular accidents after metformin administration could be expected. With those mechanisms, the effectiveness in blood hemostasis is considerable; reduction in systemic production of the tissue type plasminogen activator, Von Willibrand factor, and plasminogen activator inhibitor [13], furthermore modulation the fibrin threads formation in both diabetic and non-diabetic patients [14].

According to one recent meta-analysis, metformin is operative in reducing body weight of simple obesity (in nondiabetic, non-polycystic ovary syndrome (PCOS) patients), by reducing the absorption of glucose in the intestine, decreasing

production of glucose in the liver, and ameliorating insulin sensitivity via increasing muscle glucose uptake and use [15].

The role of metformin in the nervous system is proposed excitingly. Alzheimer is a disease with an advanced insulin resistance of the brain cell which leads to formation of the amyloid cells [16]. Undesirable oxidative damages and inactivation of AMPK pathway [17] and making delay in mitochondria programmed cell death could be mediated by metformin [18]. Besides Alzheimer, other neurological diseases like Parkinson and amyotrophic lateral sclerosis have the same mechanism.

As a result of conversion in the insulin resistance, depletion in intestinal absorption of carbohydrate and leptin secretion, and enhancing effects of glucagon-like peptide-1 on fat cells, metformin could be applied for weight reduction [19].

Additionally, prescription of metformin with antiretroviral agents (especially in HIV treatment) has been showed a reduction in their side effects like the risk of insulin insensitivity, weight obtain, dyslipidemia, and hyperglycemia [20].

In cancerous issue, there are several studies that depict the effectiveness of metformin.

One meta-analysis has concluded that metformin plays a role in the decline of liver cancer risk in type 2 diabetes patients [21]. The anti-tumorigenic sequel of metformin in pancreatic cancer [22], colorectal cancer [23], prostate cancer [24], and lung cancer [25] and its role in lowering the risk of cancer-related mortality have been proposed. From another aspect, in colorectal cancers' cell, metformin inhibits an essential energy source: adenosine A1 receptor (ADORA1) [26].

As we mentioned before, lowering the insulin levels by metformin ends in reduction in the levels of P13K pathway. (The PI3K/AKT/mTOR pathway is an intracellular signaling pathway with significant regulating function in all of the cellular stages: quiescence, proliferation, cancer, and longevity.) Moreover metformin by forcing effect on AMPK lowers the ATP ratio in cells causing switch-off of cell growth and proliferation in breast cell [27]. In breast cancer, metformin has an inhibitory effect at early stages of cell differentiation [28]; indeed, the antineoplastic effects need higher-dose consumption and more clinical evidences [29]. With those outstanding impressive mechanisms of metformin, a smaller size and slower progression of thyroid cancer [30] and advantageous effect on endometrium cancer including progesterone-resistant cancer cells [31] have been pointed.

Metformin could have an adjuvant task in treating cervical cancer, particularly in types with liver kinase B1 (LKB1) positive (a gen with tumor suppression efficacy) [32]. Eventually, there is an update study about metformin's anti-metastatic effects on aggressive malignancies like melanomas [33].

From another aspect, metformin decreases the frequency of preeclampsia, by reduction in the production of anti-angiogenic factors (soluble vascular endothelial growth factor receptor-1 and soluble endoglin) and the modification in endothelial dysfunction [34].

It must be highlighted that all of mentioned witnesses are extra glycemic effects of metformin in health jeopardies in nondiabetic patients.

3. Fertility issues

Metformin as a hydrophilic biguanide is present in many tissues like the hypothalamus, pituitary, and gonads moreover than famous places (liver, pancreas, and adipose tissues). It could be accumulating in specific tissues more than plasma level by particular transportation system, in which one of those places is the reproductive system [35]. Metformin activates the cytoplasmic protein kinase, which is a well-known enzyme: AMPK.

AMPK is a sensitive and important sensor of cellular energy homeostasis.

Hypothalamic neurons secrete gonadotropin-releasing hormone (GnRH) that stimulates follicle-stimulating hormone (FSH) and luteinizing hormone (LH) production from the pituitary gland. GnRH function in the brain has an AMPK-dependent pathway. Metformin as an AMPK activator decreases the amplitude of FSH and LH secretion.

3.1 Male reproductive system

Spermatogenesis is under noticeable hormonal regulation, especially by pituitary hormones (FSH and LH). LH stimulates the Leydig cells (LCs) to secrete testosterone and dihydrotestosterone, although FSH arouses Sertoli cells (SCs) of seminiferous tubules to maintain the cycle of spermatogenesis and inhibin secretion. Respectively, testosterone and inhibin secretion from the testis cause a negative feedback with inhibitory effects on FSH and LH. This regular system is necessary for normal spermatogenesis [36].

During spermatogenesis, the evolution process of germ cells into mature and motile spermatozoa needs specific nutrient sources which are obtained mainly from sugars (particularly glucose and fructose) and other metabolites such as lactate and citrate. Those metabolites are the most principal fuels for ATP production in germ cells and spermatozoa [37].

Moreover, production of lactate by glycolytic pathway in the SCs [38] and secretion into intratubular fluid is a necessary step for germ cell spermatogenesis. This is another energy-making way, important for motility enhancement. This process is controlled directly by glucose metabolism [39]. After primary spermatozoa production, they will store in the epididymis. Here final maturation occurs by advancement in motility function and fertilization capacity. All of those processes demand high energy and depend on glucose transporter (GLUT) proteins for carrying glucose through sperm's lipidic membrane inside the sperm cell [40]. In effect, regular and correct male fertility through this long journey is closely related to glucose metabolism.

Metformin's effect on human male reproductive function still is obscure. Extensively, current data are extracted from normal animal model studies, particularly rodents and diabetic men.

In healthy male animals, exposure to metformin displays adverse reproductive outcomes like:

1. Decrease in testosterone production [41].

2. Reduction in seminiferous tubules diameter and testis size.

3. Reduction in Sertoli cell numbers [42].

4. Decrease in sperm quality parameters [43].

In diabetic men, according to hyperglycemic state and excessive ROS production, metformin improves antioxidant environment of the testis and enhances steroidogenesis. This favorable amelioration in the testis leads to increase in concentration of motile sperm and normal morphological sperm [44]. Furthermore, metformin increases endothelial nitric oxide synthase phosphorylation [45] and the contractility in the corpora cavernosa [46], so sexual disorders like retrograde ejaculation or erectile dysfunction could be mended.

Recently, evidences of metformin efficacy in nondiabetic men are increasing. As remarked above, lactate synthesis by SCs is a crucial step in testicular metabolic cycle, which produces more desirable energy substrate for springing up germ cells and has a prominent anti-apoptotic effect [47]. Also, some studies showed that metformin plays a role as a suppressor of complex I of the mitochondrial electron transport chain that directly decreases oxidative metabolism and accordingly increases anaerobic respiration and lactate secretion [48].

Surprisingly, adding metformin in cryopreservation media during sperm freezing practice (for fertility preservation) reduces sperm permanent damage and improves the rate of success in fertilization process and decreases the number of abnormal zygotes after in vitro fertilization [49].

3.2 Female reproductive system

As it is well-known, metformin has a crucial role in PCOS pathogenesis amelioration and not surprising the large number of studies about its efficacy and widespread utilization. But, when we are looking for its usage in non-PCOS infertile or subfertile woman, unexpectedly, there is scanty study about it.

Insulin resistance could have significant negative role in various conditions such as stress [50], aging [51], obesity [52], depression [53], and inactive lifestyle [54]. Infertile women often have one of those conditions. Moreover, ovarian dysfunction induces "stress response mechanism" owing to abnormal cortisol secretion and increased level of catecholamines [55]. Besides that, by enhancing in insulin-like growth factor-binding protein-1 and glycodelin level, uterine vascularity and blood flow could be increased [56].

Those beneficial effects had been demonstrated in a study on about 200 patients (non-PCOS) with repeated IVF failure. In this study in a period of 8–12 weeks, low-dose (500 mg/day) metformin administration before IVF cycle significantly increases the pregnancy rate by improving in oocyte quality and endometrium, receptivity [57].

In another bovine study, it was shown that IGF-1 has a dual positive role in follicle regulation which increases FSH effectiveness as an autocrine regulator of granulosa cell growth that could illustrate metformin worth in infertility treatment procedures [58]. Moreover, in vitro experiment studies show that metformin could decrease the progesterone [59] and estradiol [60] secretion from granulosa cells and androstenedione [61] from theca cells.

4. Conclusion

As we reviewed in this chapter, metformin did not equal to NIDDM and PCOS, anymore. In all of the mentioned fields, researches are increasing more and more.

Conflict of interest

The author declares no conflict of interest.

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