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ANTI-AGING PROPERTIES OF METFORMIN

Anna Łopuszyńska[1], Mateusz Pawlicki[1], Magdalena Kozioł[1], Aleksandra Krasa[1], Ewa Piekarska[1], Halina Piecewicz-Szczęsna[2]

[1]Student Scientific Association at Department of Epidemiology and Clinical Research Methodology Medical University of Lublin, ul. Radziwiłłowska 11, Lublin 20-080, Poland

[2]Department of Epidemiology and Clinical Research Methodology of the Medical University of Lublin, ul. Radziwiłłowska 11, Lublin 20-080, Poland

Corresponding author: Anna Łopuszyńska, lopuszynskaania@gmail.com

ORCID ID:

Anna Łopuszyńska https://orcid.org/0000-0001-5133-4180, lopuszynskaania@gmail.com

Mateusz Pawlicki https//orcid.org/0000-0001-8318-6573, pawlak32@gmail.com

Magdalena Kozioł https://orcid.org/0000-0002-8671-5968, magdalena.koziol@icloud.com

Aleksandra Krasa https://orcid.org/0000-0002-0733-202X, ola.AK62@gmail.com

Ewa Piekarska https://orcid.org/0000-0002-4954-379X, piekarskaewaa@gmail.com

Dr n. med. Halina Piecewicz-Szczęsna https://orcid.org/0000-0002-0573-7226, halpiec@gmail.com

Abstract

Introduction: Life expectancy of human population is being constantly prolonged, hence there is a lot of research into drug that will prevent the effects of aging. There are many reports that metformin, which is a drug used in type 2 diabetes, has anti-aging effects. It belongs to the group of biguanides and has been used since the 1950s. It is a relatively safe, cheap and effective drug, which makes it a

promising subject for many studies. The purpose of this review is to present the latest developments in this field.

Material and methods: PubMed scientific base was searched using following keywords: metformin, aging, anti-aging, in years 2017-2021.

Results: Numerous studies show that metformin has an impact on aging through the nutrient pathway, AMPK signaling pathway, and its effects on reactive oxygen species. In addition, it has an anti-cancer effect, inhibiting, among others, rectal cancer cells and p53 mutant colon cancer. Research in rodents has shown that this drug has anti-aging effects on many organs, including the CNS, ovaries, prostate, heart muscle and skin.

Conclusions: Metformin, which is the most commonly used oral drug in type 2 diabetes, has many other mechanisms of action. Its anti-aging effect works on many organs in our bodies, which gives hope to find an anti-aging substance. However, multicentre, randomized trials are needed to determine the exact anti-aging dose, its possible side effects, and effects on various organisms.

Key words: metformin, anti-aging, aging

Introduction:

Life expectancy of people around the world is increasing rapidly. Over the past 200 years it was around 2.5 years per decade. Hence natural selection was unable to maintain the evolutionary efficiency of elderly people. Aging is a process that slowly deteriorates many bodily functions. It is also a risk factor of many chronic diseases, including cancer, dementia and cardiovascular diseases [1].

Metformin, is the first-line drug in type 2 diabetes, which belongs to the biguainide group and has been used since the 1950s. It improves glycemic control without inducing hypoglycaemia or weight gain [2]. There are more and more reports that this drug, apart from its anti-diabetic effect, also has many other functions. The ability of this biguanide to extend life expectancy has led to numerous studies determining its effectiveness, safety, effects and mechanisms of action [3].

Methods:

PubMed research base was searched using following keywords: metformin, aging, anti-aging, in years 2017-2021.

Description of knowledge:

Mechanism

Metformin, used for over 60 years to treat type 2 diabetes, is a promising anti-aging drug because it is cheap, effective, and relatively safe. The drug has been found to extend the life of mice and C. elegans [4]. There is growing promising evidence that it can regulate aging through regulatory changes in the (epi)genome architecture [5]. It owes its anti-aging effect to many different mechanisms, one of which is the nutritional pathway. Metformin lowers level of insulin and glucose in blood and increases insulin sensitivity, which lowers level of AGE, which is a marker of aging. This drug also affects the concentration of ROS, which accelerates aging by damaging genes or proteins. In the case of ROS

accumulation, metformin induces the production of antioxidant proteins such as SIRT3 or GPx7, and thus reducing the level of oxidative stress. Another known anti-aging mechanism is the inhibition of mTOR activity through the activation of AMPK. This process leads to the activation of autophagy, which prevents the accumulation of damaged proteins [6].

There are more and more reports that metformin has an anti-cancer effect and inhibits in vivo and in vitro, inter alia, rectal cancer cells and p53 mutant colon cancer cells. It has also been noticed that diabetic patients treated with this drug have 30% fewer cancers such as breast cancer, stomach cancer or prostate cancer. In the case of pancreatic cancer an increase in the survival rate has been noticed [7].

In terms of its influence on genes important in aging, metformin was highly rated in lung, muscle, nervous and adipose tissue, which suggests its possible anti-aging effect on the whole organism [8].

Organ systems

Stem cells are used in regenerative medicine to create and repair tissues and organs. Due to reports on the anti-aging effect of metformin, many studies have been conducted to assess its effect on stem cells in order to improve the effect of their action. The review by L. Jiang (2020) summarizes all up to date discoveries on this topic. Studies show that metformin has an effect on the differentiation of stem cells and progenitor cells. This drug may promote osteogenic differentiation of stem cells and osteogenic progenitor cells, mainly via the AMPK pathway and Runx2-related signaling pathways. This effect is associated with increased proliferation and migration of cells, alkaline phosphatase activity or increased expression of osteoblast marker genes. A dose of 50-100 μmol / l of metformin was found to be optimal.

In the case of adipocytes (adipose tissue stem cells) metformin inhibits their differentiation, which results in inhibition of cell proliferation, generation of lipid droplets and adipocyte gene expression. It exerts this action via the AMPK signaling pathway.
It is suggested that metformin promotes the differentiation of gastric epithelial progenitor cells into parietal cells secreting hydrochloric acid by activating AMPK, which may be of key importance in the prevention of gastric cancer [9].

M. Kodali et al. (2021) investigated the effect of metformin administered by oral gavage at a dose of 100 mg / kg once daily for 5 days a week for 10 weeks in 18-month-old (late middle age) mice. Research suggests that this drug improves brain functioning - pattern separation, location memory, recognition. In the case of hippocampus, modulation of microglia to the favorable anti-inflammatory phenotype of M2 was noted, as well as a decrease in astrocyte hypertrophy. Moreover, there was a decrease in the pro-inflammatory cytokines TNF-α and IL-1β, and the chemotactic cytokine MIP-1α in the hippocampus, which, at elevated concentrations, can impair synaptic transmission and plasticity in the hippocampus and, as a result, memory function. There was also an increased autophagy due to AMPK activation and inhibition of mTOR signaling, which is responsible for the proper maintenance of cognitive functions. However, no increase in neurogenesis in the hippocampus was observed [10].

Another study by X. Zhu et al. (2020) focused on the effect of metformin administered to elderly mice through the tail vein at a dose of 0.5-15 mg / kg over a period of 10 months. There is a decrease in glucose uptake by the brain appearing with age and this results in decreased oxygen glycolysis in brain and reduced blood flow. This study suggests that metformin may increase glycolysis in older mice by increasing the expression of GAPDH mRNA, which is an important glycolytic enzyme and in the presence of NAD + converts glucose-derived glyceraldehyde-3-phosphate into 1,3-bisphosphoglycerate ultimately increasing angiogenesis and neurogenic potential NSC (neural stem cell). Thus, the beneficial effects of this drug on cognition may be related to the restoration of vascular integrity, improved blood flow in the brain, and activation of neurogenesis.

Additionally, it has been noticed that long-term oral treatment with metformin carries many side effects (e.g. cataracts, dermatitis, tumors) and may be associated with an effect on the intestinal microbiome. However, intravenous administration bypasses this route and does not affect the bacterial flora. Nevertheless, further research into the mechanism of this phenomenon is needed [11].

A study by C. Li et al. (2020) performed in vivo in the hearts of elderly mice and human heart samples showed that treatment with metformin can inhibit myocardial necrosis during aging. Age-related accumulation of p62, caused by impaired autophagy, facilitates the activation of RIP1-RIP3, which increases the risk of I / R (ischemia-reperfusion) damage to the heart. Autophagy, on the other hand, is a very important process as it reduces injuries and preserves myocardial function during ischemia. Treatment with metformin has been found to have a positive effect on autophagy and reduce p63 binding to necrosomes, resulting in a decrease in mortality. These findings suggest that this substance may be a promising cardioprotective drug [12].

Menopause is a permanent physiological cessation of the menstrual cycle, which results in the termination of the ovarian synthesis of estrogens and progesterone. These changes are associated with osteoporosis, cardiovascular disease, cancer, obesity, Alzheimer's disease, etc. Therefore, research is ongoing to delay the aging of ovaries. X. Qin et al. (2019) investigated the effect of an average metformin dose on middle-aged female mice. 28-week-old mice (age corresponding to a 37-year-old female) were fed with 100 mg / kg metformin for 6 months and were then tested and compared with a control group. It was noticed that after six months, 78.9% of the tested mice had a regular oestrus cycle, while in the control group this percentage was only 38.5%, which may suggest that metformin prevents ovarian aging. Additionally, tested animals had a significantly higher ($p < 0.05$) ovarian reserve. P16, is a molecule that prevents the progression of the cell cycle from G1 to S phase. Its expression increases with age and in drug-treated mice study, its levels were lower. On the other hand, activated SIRT1 protein inhibits oxidative damage and the production of ROS during aging. Its level was found to be higher in the studied individuals. This study suggests that metformin may be a promising agent for women's health [13].

Hyperglycaemia and insulin resistance, such as those found in obesity, the metabolic syndrome and type 2 diabetes (T2DM), are associated with an increased risk of BPH (benign prostatic hyperplasia). In South Korea, a study (2019) was conducted on a group of 211,648 men with this disease. The men were divided into three groups: without type 2 diabetes (197722), with diabetes treated with metformin (11059) and with diabetes not treated with metformin (2867). The progression of BPH was considered to be the performance of prostatectomy and in the groups of men with coexisting T2DM, a significantly lower degree of this surgical intervention was observed in people using metformin. These results may suggest that this biguanide may have an inhibitory effect on the development of BPH. This may be explained with the fact that metformin weakens the IGF-1 signaling pathway, which is important for the growth of prostate epithelial cells, as well as for the regulation of the interaction of the stroma with the epithelium, through the paracrine pathway between IGF-1 and its receptor in the prostate. Estrogen-α receptor proliferative and anti-apoptotic responses were reduced during treatment with metformin. In the case of the estrogen-β receptor, the pro-apoptotic response was increased. Results of this study are very promising, but more research is needed to rule out the effects of other medications used by patients and other confounding factors [14].

Skin wounds are one of the most common soft tissue injuries, and aging is associated with an increased risk of chronic non-healing wounds that are clinically burdensome and lack an effective therapeutic agent. In the rodents studies of P. Zhao et al. (2017), topical metformin was found to be a promising drug for wound healing in both younger and older individuals. Metformin was found to positively influence angiogenesis via the AMPK activation pathway. AMPK signaling, which was mainly present in CD31 + endothelial cells, stimulates the expression of vascular endothelial growth factor, which is essential for angiogenesis. Moreover, in the case of aging skin, the rejuvenating effect

was significant. This study suggests that metformin may be a promising regenerative agent in skin damage [15].

In aging skin, the level of glucose increases, while the metabolites of PPP (pentose phosphate pathway) are lowered, which is associated with a decrease in the synthesis of glycerolipids. The reduction of NADPH, which is a cofactor in the synthesis of fatty acids, may reduce the regeneration of the lipid barrier in the elderly. Accordingly, modulating the activity of G6PD (glucose-6-phosphate dehydrogenase), which is the first step in PPP metabolism of glucose, may counteract the aging-induced decline in lipid barrier regeneration. Additionally, G6PD activation can protect against UV and oxidative damage and contribute to their repair. The study noted that the G6PD activity of the epidermis increased 2 days after the administration of metformin. However, it is not known what the mechanism of this phenomenon is. The AMPK activation / inhibition of the mitochondrial complex I is considered the most likely. The results may suggest that this drug has a positive effect on aging skin [16].

All these reports are prospering and give hope to find a suitable anti-aging drug. However, it should be borne in mind that all the mechanisms by which metformin works are not known and little is known yet. In addition, aging is not the same phenomenon for everyone, so different people will react differently to the drug and therefore each patient should be treated individually. Hence, there is a need for multicentre, randomized trials on this topic. Moreover, metformin is eliminated from the body unchanged, so attention should be paid to the consequences of its use in the event of changes in the ecosystem [17].

What is more, studies are conducted mainly in rodents, which makes it difficult to scale the appropriate dose of metformin for humans from laboratory studies in animals. Additionally, many studies show the difference between the use of the drug in female and male rodents, which requires further diagnosis [18].

Conclusions:

Metformin, which is the most commonly used oral drug for type 2 diabetes, has many other mechanisms of action. Its anti-aging effect works on many organs in our bodies, which gives hope to find an anti-aging substance. However, many detailed, multicentre, randomized trials are needed to determine the exact anti-aging dose, its possible side effects, as well as its effects on various organisms.

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