

# New pharmacotherapeutic aspects associated with the use of Metformin

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## Introduction

Metformin, one of the oldest but still first-line oral antidiabetic agents, has become the medication with steadily increasing potential therapeutic indications. It is generally well-tolerated with minimal side effects and is affordable. This drug has been increasingly used in off-label indications, such as polycystic ovarian syndrome, obesity, and metabolic syndrome (Aljofan and Riethmacher, 2019). Also, metformin has been found to decrease the rate of age-related illness progression improving longevity, especially in the setting of cancer. Metformin also retards aging in model organisms and reduces the incidence of aging-related diseases such as neurodegenerative disease (Soukas et al., 2019). Positive results show that the risk of developing lung cancer is lower in patients with chronic metformin use (Yao et al., 2019). A Korean study of patients diagnosed with diabetes and hepatocellular carcinoma (a type of liver cancer) who underwent malignant tissue removal surgery showed that those treated with metformin had significantly higher survival rates than those with other hypoglycemic agents (Seo et al., 2016). A study in Italy aimed to compare the effects of metformin and clomiphene as the first drug of choice in women without ovulation and with polycystic ovary syndrome (PCOS) (Palomba et al., 2005). Pregnancy was statistically better in the metformin-administered group and abortion statistics were lower in that group. Metformin can improve ovulation and regulate the menstrual cycle, which means a greater chance of pregnancy. Our study aimed to examine the off-label use of metformin in the Republic of North Macedonia population.

## Materials and methods

We prepared an anonymous survey questionnaire to evaluate the off-label use of metformin in our population. According to our knowledge, this is the first such examination in our country. Including criteria for patients in this study was chronic metformin use. Patients filled out the questionnaire with the help of fellow pharmacists in pharmacies from Bitola, Debar, Ohrid, Skopje, and Veles while taking their chronic therapy, which includes metformin. The first questions were about the gender and the age of the patients. In the questionnaire, patients had to indicate which dose of metformin they were taking and the dosing frequency. The final set of questions was related to their side effects while taking this therapy and whether they had any other illness besides type 2 diabetes. Answers offered were dementia, depression, cancer, cardiovascular disease (specifying which one), hypo/hyperthyroidism, acute/chronic kidney disease, and peptic ulcer.

## Results and discussion

Seventy patients were interviewed, 36 (51.4%) were women, and 34 (48.6%) were men. Five respondents were in the category up to 20 years, 16 in the group up to 40 years, and the most significant number of patients (49) were in the category over 40 years. The most frequently used dose was 500 mg metformin. The positive fact is that there were a large number of patients - 23 out of a total of 70 who had no side effects, and from the rest offered, the results only confirmed what is mentioned in the Patient Information Leaflet. The GIT problems are in the most significant number. Other recorded side effects were: change in taste, general feeling of malaise with severe fatigue, shortness of breath, redness of the skin, itching and

urticaria, and low levels of vitamin B<sub>12</sub> in the blood. Related to the last question about “History of diseases”, the most significant percentage of patients, or 51%, answered that they have cardiovascular disease and type 2 diabetes. 17% have depression and the same rate for hypo/hyperthyroidism, while 10% have dementia. Within this question, 3% of kidney diseases (acute/chronic) and peptic ulcer were registered, while there is not a single answer that is 0% for cancer patients who chronically use metformin. In our study, two patients up to 20 years were taking metformin for treatment of PCOS.

Recent studies suggested multiple potential mechanisms that support the concept of cardiovascular protection with metformin beyond those provided by reduced blood glucose, including weight loss, improvements in haemostatic function, reduced inflammation, and oxidative stress, and inhibition of key steps in the process of atherosclerosis (Hasanvand, 2022). A possible explanation for this maybe we can find in the mechanism of action of this drug. Activating the AMP-activated protein kinase (AMPK) signaling pathway, a mechanism of how metformin works, can be positive in cardiovascular disease. Its activity reduces mitochondrial fission induced by Drp1 protein by lowering its levels (Wang et al., 2017). Anti-aging effects of metformin also can be correlated with the mechanism of action of metformin. Activation of the AMPK pathway and inhibition of mTOR pathways are possibilities in which metformin can serve as an anti-aging agent. Additionally, studies showed that activating the AMPK signaling pathway suppresses inflammatory cytokines such as TNF $\alpha$ , IL-6, IL-1 $\beta$  and NF- $\kappa$ B. (Saisho Y., 2015).

Due to this positive effect of activating the AMPK pathway, clinical trials are increasingly aimed at revealing the efficacy, survival time, developmental time, or cessation of carcinogens when using metformin, and in combination therapy that is inserting metformin together with some cytostatic or radiation. A Brazilian study in phase 2 inspired by preclinical studies showing that metformin has an anti-tumor effect in colorectal cancer (CRC) was the first step in combination therapy with metformin with 5-fluorouracil and demonstrated results in delivered survival in patients. Further trials are needed to confirm these results, particularly in obese patients with CRC. (Miranda at al., 2016).

## Conclusion

Results from our survey presented that metformin in North Macedonia is mostly used for the treatment of type 2 diabetes mellitus as it is indicated in the Summary of Product Characteristics, and only two patients reported its off-label use. Many studies have investigated the role of

metformin in the treatment of various diseases, including inflammatory diseases, autoimmune diseases and cancer. Since its therapeutic use, even at high doses, does not lead to severe side effects, metformin has a significant role in either treating various diseases or reducing their symptoms.

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