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 quite affordable. This drug has been increasingly used in off-label indications (Aljofan M. and Riethmacher E., 2019) such as:

- ❖ polycystic ovarian syndrome (PCOS);
- ❖ obesity;
- ❖ metabolic syndrome.

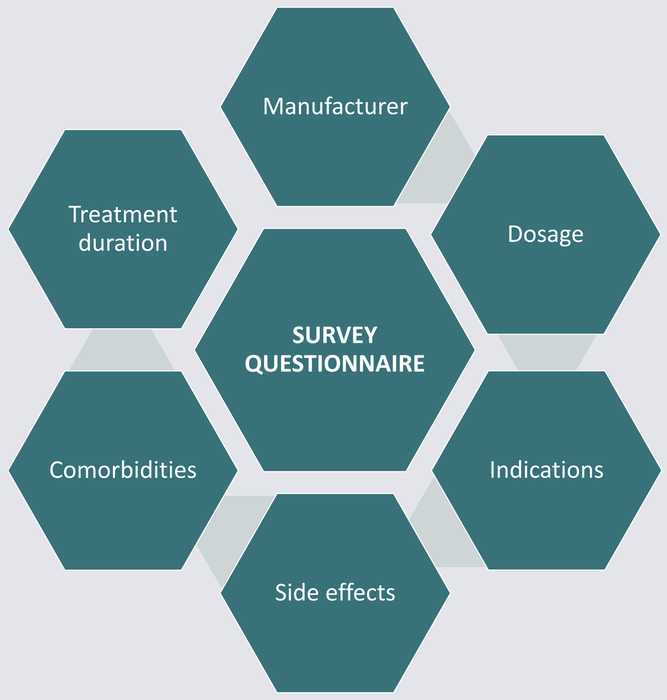
Additionally, numerous studies suggest that metformin is associated with following positive outcomes:

- ❖ improved longevity and decelerated aging in model organism;
- ❖ reduced incidence in neurodegenerative diseases;
- ❖ lowered risk of developing lung cancer;
- ❖ enhanced survival rates in patients with hepatocellular carcinoma;
- ❖ beneficial cardiovascular effects;
- ❖ better regulation of menstrual cycle and greater chances of pregnancy.

The objective of our study was to examine the possible off-label benefits related to the chronic use of metformin in the population of Republic of North Macedonia.

Materials and methods

An anonymous survey questionnaire was disseminated to patients who were on therapy with metformin, in pharmacies in Bitola, Debar, Ohrid, Skopje, and Veles. According to our knowledge, this is the first such examination in our country.

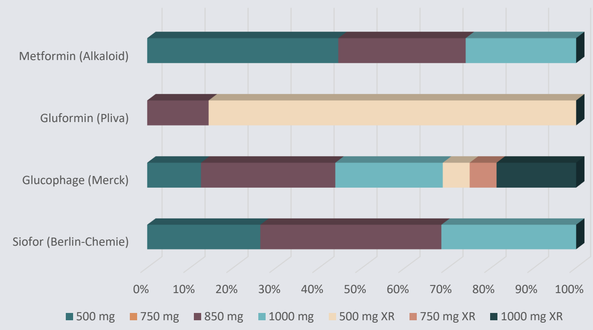


Results and discussion

70 patients treated with metformin (51.4 % women) were interviewed.

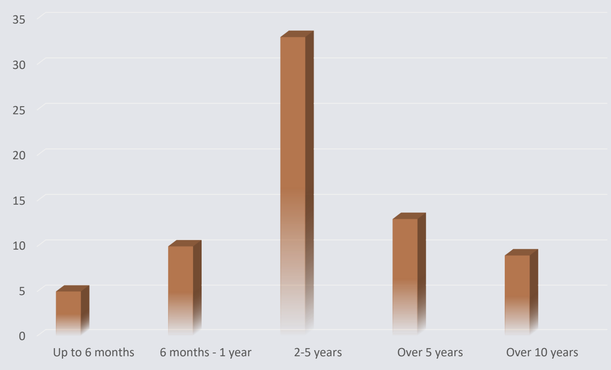
Five respondents were in the category up to 20 years, 16 in the group from 20 to 40 years, and the most frequent distribution of patients (49) were in the category over 40 years.

❖ *Dosage*



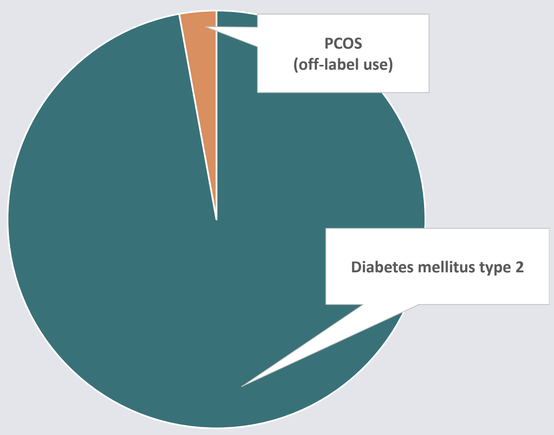
The most frequently commonly used dose metformin among responders most used dose was metformin 500 mg.

❖ *Treatment duration*



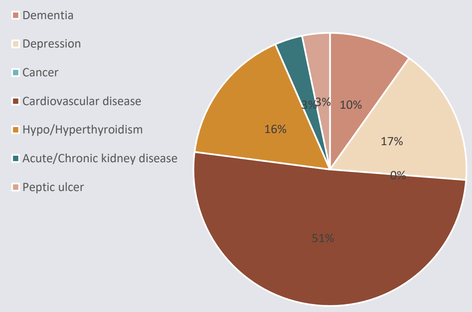
Vast majority of the patients were using metformin for more than one year.

❖ *Indications*



97.1% patients were using metformin for treatment of type 2 diabetes mellitus, while only 2.9% used it for PCOS (off-label use). 47 of 70 patients reported side effects, all of which are included in the Reference Information for metformin.

❖ *Comorbidities*



The most frequent comorbidities were cardiovascular diseases (51%).

❖ New pharmacotherapeutic aspects

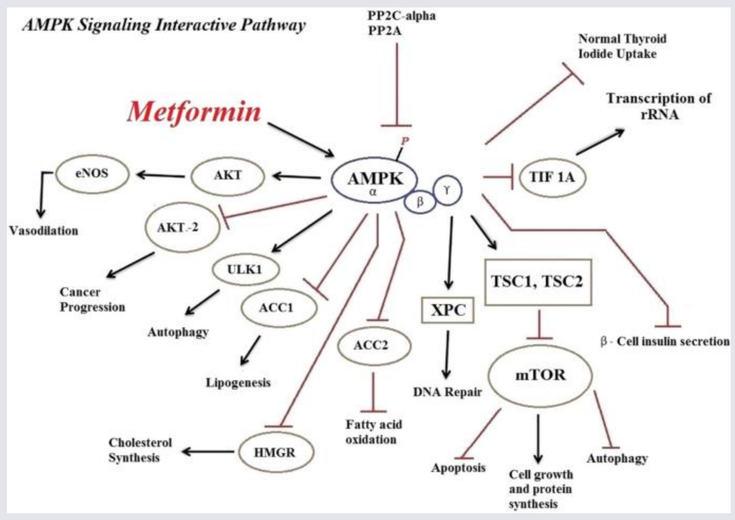


Figure 1. The role of AMPK-dependent pathways in cellular and molecular mechanisms of metformin. (Hasanvand A., 2022).

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.

Most of these effects have been associated with stimulation of AMP-activated protein kinase (AMPK)/inhibition of Mammalian Target of Rapamycin (mTOR) by metformin, and such mechanisms are relevant to the clinical therapeutic effects of metformin (Wang et al., 2017). Additionally activating the AMPK signaling pathway suppresses inflammatory cytokines such as TNFα, IL-6, IL-1β and NF-κB. (Saisho Y., 2015).

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. A considerable number of these investigations have revealed that the capacity of metformin to activate AMPK and also the consequent activation or inhibition of different factors by metformin enable it to alter the pathological pathways of the disease, direct cell differentiation, and moderate the inflammatory conditions. 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.

References

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