

COVID-19: Can Metformin Drastically Reduce the Number of Deaths?

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ABSTRACT

To address the current pandemic due to Sars-Cov-2, there are various strategies concerning social behaviors such as social distancing and lockdowns, vaccines, and targeted antivirals. Our further proposal is to identify an already existing drug that is safe and has therapeutic characteristics that are useful in terms of Covid-19. This drug is Metformin, the most widely used anti diabetic drug that has already been proven effective in areas other than that for which it was created and has demonstrated proven safety over many years of administration to a population of hundreds of millions of people. We review the medical literature attesting to the important characteristics of metformin as a drug against obesity, cancer, aging, and cognitive deterioration.

The proposal to use metformin as an anti-Covid-19 drug, which would reduce morbidity, mortality, and organ damage, is based on its recognized ability to modulate and normalize the production of inflammatory cytokines, including interleukin 6, the overproduction of which, produced by the intra-abdominal fat in obese or overweight patients, is the cause of very serious outcomes in Covid-19 patients. To validate the above statement, we report a retrospective analysis carried out in Wuhan on patients hospitalized for Covid-19 from January 27, 2020 to March 24, 2020, in which diabetic patients treated with metformin and diabetic patients without metformin treatment were examined. At the time of admission, there were no significant differences between the two groups in terms of sex, age, underlying disease, clinical severity, and oxygen support category. Anti-diabetic treatment with metformin was associated with a significant decrease in mortality, statistically four times less, than in diabetic patients not treated with metformin.

Keywords

Metformin, Metabolic Syndrome, Covid-19, Sars-Cov-2, Cytokines, Cytokine Storm, Interleukin 6, IL-6, Interstitial Pneumonia, Obesity, Overweight, Visceral Adipose Tissue, VAT, Visceral Abdominal Fat, Waist Circumference, Waist-Hip Ratio, WHR, Bio-Impedancemetry, Adipocyte, Myocyte, Muscle Metabolism, Biguanide, Diabetes, Antidiabetic, Insulin Resistance, Hyperinsulinemia, Body Mass Index, BMI, Translational Medicine, Host-Directed Therapy, Galega Officinalis, Jean Sterne.

There is no person in the world who is not wondering when and how the nightmare of Covid-19 will end [1].

It will probably be the "how" to define the "when" and, about the "how", the hypotheses are manifold and not mutually exclusive [2].

First hypothesis: One day the virus will die out by itself, or it will lose much of its virulence. This does not exclude taking other measures in the meantime to prevent the scenario from becoming dramatic, in addition to not being able to predict the timing of the "when" [3].

Second hypothesis: There will be a large-scale availability of a specific antiviral [4] that defeats the Sars-Cov-2 virus [5].

Third hypothesis: The virus can be brought to extinction by social distancing [6], precautions and protections (washing hands, using masks, etc...) [7], and quarantining the sick and those who have recently come into contact with them. This measure has proven successful in slowing the spread of the virus, but not in reducing

it to zero. Reducing the possibility of contagion to zero would require a total and absolute commitment on the part of each of us, with very heavy psychological, social, and economic costs – a total lockdown to be prolonged over time until the virus has died out by itself. The implementation of a program like this is further made difficult by the geographic spread of the virus and, consequently, by the extreme difficulty in doing this worldwide [8].

Fourth hypothesis: It concerns a safe and effective vaccine [9-13] and this is a new challenge [14] for the scientific world.

Fifth hypothesis: Perhaps among the drugs already present in our vast pharmaceutical world, there is one that is useful in tackling the pandemic due to Sars-Cov-2.

For over 60 years, there has been a drug, perhaps the most prescribed in the world that has already been used by hundreds of millions of people. For each of these people, once therapy has started, it lasts for a lifetime, i.e., in many cases, for tens of years. We are talking about Metformin, the anti-diabetic drug par excellence [15] for type 2 diabetes mellitus, the affliction of modern times, one that usually affects obese people over 40 years of age. Metformin is now also used [16] against aging, cancer, and cognitive decay, as we will see later.

It all began with a plant that has been used in folk medicine for centuries: the *Galega Officinalis*, commonly known as "French lilac" or "goat's-rue" [17]. This plant contains alkaloid chemicals called biguanides. In the 1920s, by chemically synthesizing the various biguanides, metformin was produced, a new biguanide not present in the plant. It was first described in 1922 in a scientific article by Emil Werner and James Bell [18]. In 1929, Slotta and Tschesche had already discovered its function on blood sugar [19], but their study fell by the wayside because the use of insulin was king. It was then the French diabetologist Jean Sterne [20] who studied the anti-hyperglycemic properties of the alkaloids obtained from *Galega Officinalis*, whose chemical structure is correlated with metformin. Later he worked for Aron laboratories in Paris and re-investigated the use of metformin and other biguanides. So it was Sterne who tried metformin on humans for the treatment of diabetes and called the drug "Glucophage" (which means "sugar eater" in Greek). His studies were published in 1957 [20,21]. Metformin, registered in the British National Formulary in 1958, began to be marketed in the UK by Rona, a small subsidiary of Aron. The great interest in metformin as an anti-diabetic occurred in the 1970s. In 1972 it was approved in Canada [22]. In the US, the Food and Drug Administration (FDA) approved it in 1994. The result is that metformin, which has been on the market for more than 60 years, is the most prescribed anti-diabetic drug in the world [21].

In recent decades, metformin, as a specific anti-diabetic drug, has surprisingly revealed itself as an anti-cancer agent [23], decreasing the incidence of cancer and its related mortality. Further studies have found that the use of metformin is a positive factor against breast [24-26], ovarian [27], lung [28], and prostate [29] cancer.

This is not surprising because hyper insulinemia and high blood sugar, for which metformin has a regulatory and normalizing effect [30], are essential for the metabolism of cancer cells and that of inflamed tissues. In fact, the diagnostic examination of PET (Positron Emission Tomography) is based on sugar metabolism using a radioisotope linked to a sugar molecule [31].

Furthermore, metformin has been shown to be useful in improving the clinical and biochemical characteristics of polycystic ovary syndrome [32].

Metformin also has a beneficial effect on several cardiovascular risk factors including dyslipidemia [33]. For a while now, it has been found that metformin reduces hypertension, both total and LDL cholesterol, triglycerides, fasting plasma insulin, and the levels of peptide C, which indicates how much insulin has been produced in the blood, even in middle-aged, non-diabetic, non-obese, and non-smoking hypertensive subjects. In fact, insulin resistance and hyper insulinemia may play an important role both in the development of hypertension and in the metabolic alterations that accompany it [34]. According to some studies, metformin also has a beneficial effect on pulmonary hypertension [35].

Continual treatment with metformin has also been shown to be useful in the prevention of atherosclerosis and vascular senescence [36]. It has also been associated with a reduced size of myocardial infarction [37], a reduced risk of stroke [38], an improvement in stroke treatment [39], and a slowing of cognitive decline, reducing the incidence of dementia [40]. The action of metformin has proven to be useful in non-alcoholic fatty liver disease associated with obesity [41] and against the inflammation associated with obesity. This anti-inflammatory mechanism occurs through the modulation and normalization, thanks to metformin, of the production of proinflammatory cytokines, which are produced in excess in the obese [42]. The ability of metformin to modulate and normalize the production of inflammatory cytokines is an additional indication for its continual intake in this pandemic context. In fact, a dysregulated and excessive release of proinflammatory cytokines with a loss of regulatory control of their production both locally and systemically has been seen to be connected with the severity of the course of Covid-19 [43]. The modulation and normalization of cytokine production with the continual intake of metformin would occur automatically without negative side effects on immunity, whereas the use of other drugs not without side effects aimed at directly reducing the production of cytokines would require a thorough and accurate evaluation to establish which drug should be used as well as the single dosage [44].

Metformin, given its use for over half a century on a huge number of diabetics, has long been shown to be a very safe drug [45] whose side effects, which have been gradually discovered, seem not to be negative but rather fundamentally positive for the health of even non-diabetics: anticancer, anti-obesity, and anti-aging (improving quality of life and lifespan) [46-48]. For some time, metformin has been used for these beneficial effects even on people who are not diabetic – a typical example of translational medicine [49],

which is the use of a therapy in a multidisciplinary field and not only strictly for the specialty for which it was created [23]. This use of metformin is strengthened by the fact that the safety of this drug has already been proven by the incredible number of diabetic patients (several hundreds of millions) who have taken it and by the duration of its intake, which is usually throughout their lifespan [45].

Furthermore, metformin has also been shown to be a safe drug in patients with other diseases, such as liver [50] and kidney disease [51].

Obviously, like all drugs, it must be taken under medical supervision and an analysis of creatinine in the blood (a test recommended by default in routine tests for everyone, including healthy people) must be performed to monitor renal function, which, if insufficient, requires dosage adjustments of the drug due to its decreased elimination in the urine. A check of vitamin B12 in the blood is also useful (another test that should be performed by default for everyone). A vitamin B12 malabsorption can be associated with long-term metformin treatment [52], but its absorption can improve with dietary calcium supplementation [53].

Metformin is contraindicated in cases of alcohol abuse – both overt alcoholism and the excessive alcoholic load on Friday and Saturday evenings – due to the increased risk of lactic acidosis, a risk that is very rare and almost exclusively possible when proven medical contraindications already exist for pre-existing severe organ damage [54]. It is recommended to start with a daily dosage of 500 mg at breakfast, then increase to two doses (breakfast and dinner), and eventually reach three doses (breakfast, lunch, and dinner). The dosage for an adult is usually 1.5 grams per day and should never exceed 3 grams per day. In most cases, taking metformin does not cause any problems. In the initial phase of taking the drug, in a small percentage of cases, there may be intolerance (with a feeling of nausea or gastralgia and/or diarrhea), which can often be resolved by the gradual introduction of the dosage, the distribution of the dosage throughout the day, or by switching to the “slow” formulation or to the powder formulation such that the oral solution can be dissolved in water.

But let's return to Covid-19.

There is an article concerning the analysis of 150 male and female patients – aged between 22 and 97 years (average age 64 ± 16 years) of which 64.7% were males – who were admitted to the emergency room of Sant'Andrea Hospital in Rome in March 2020 diagnosed with Covid-19 [55]. All patients had undergone two nasopharyngeal swabs at 24-hour intervals, and the samples were tested to confirm the diagnosis (Charité, Berlin, Germany) of Sars-Cov-2 by real-time reverse transcriptase (RT-PCR). All patients had chest CT scans, thus, it was possible to quantify the amount of visceral adipose tissue (VAT) by selecting the first slice of the CT scan in which only the abdomen was visible without the lung bases. The results of this study show that visceral abdominal fat

is an indicator of more severe clinical outcomes for Covid-19 patients.

Excess visceral adipose tissue (VAT) is the main secretor of cytokines, including interleukin 6 (IL-6) [56]. This capacity of the adipocyte could be one of the reasons why the obese have higher levels of C-reactive Protein (CRP) – value used in medical diagnostics to assess the level of inflammation – than those who are non-obese [57]. In retrospect, interleukin 6 levels increased in the non-survivors of Covid-19 [58].

Metformin has a beneficial effect on body weight and body composition, and treatment with metformin resulted in a significant reduction in visceral fat mass [59]. Long-term treatment with metformin on patients with abdominal obesity, in association with a low-calorie diet, led to a greater reduction in body weight and abdominal fat, compared to the placebo case. The reduction particularly concerned visceral deposits, with a greater reduction in abdominal circumference. As prevention of Covid-19 and its complications, there could therefore be an indication for continual treatment by metformin in patients who are obese or overweight [60].

Furthermore, it was shown that metformin led to a significant improvement in insulin resistance and the function of the beta cells of the pancreas that produce it [61]. Metformin is associated with the normalization of blood glucose and not with hypoglycemia because it does not stimulate insulin secretion [33]. Metformin restores normal insulin production by also reducing basal insulin if it is excessive [61]. Let us not forget that hyper insulinemia induces inflammation, so much so that by some it would be considered a risk factor for Alzheimer's disease [62].

Metformin, with its complex mechanisms of actions – reduction of hepatic neoglucogenesis, tendency to normalize blood glucose, reduction of insulin resistance, to name a few – has proved useful, as already mentioned, against obesity and its associated inflammation, thanks to the decrease in proinflammatory cytokines [48].

There is further evidence of the advantages of the continual use of metformin also for the Covid-19 pandemic – of which it reduces morbidity, mortality, and damage to organs – in addition to the recognized benefits against aging, cancer, and cognitive deterioration in the elderly.

To validate the above, we report a retrospective analysis carried out in Wuhan on patients hospitalized for Covid-19 from January 27, 2020 to March 24, 2020 [63]. This analysis studied 104 diabetic patients treated with metformin and 179 diabetic patients without metformin treatment. At the time of admission, there were no significant differences between the two groups in terms of sex, age, underlying disease, clinical severity, and oxygen support category. The metformin group had a slightly higher fasting blood glucose level than the non-metformin group. In both groups, blood glucose

was effectively controlled after admission. Length of hospital stay did not differ significantly between the two groups (21.0 days for the metformin group versus 19.5 days for the non-metformin group). However, during the hospital stay, the mortality rate of the group treated with metformin was significantly lower (3/104, i.e., 2.9%) compared with the group not treated with metformin (22/179, i.e., 12.3%). Therefore, anti-diabetic treatment with metformin was associated with a significant decrease in mortality, statistically 4 times less, than in diabetics not treated with metformin.

The continual intake of metformin (anti-diabetic, anti-aging, and antitumor drug that also works against senile cognitive decay) shows a medical indication that extends to the current Covid-19 emergency because by avoiding the hyper inflammatory response resulting from an excessive production of cytokines, robustness is boosted in the face of Sars-Cov-2. If in the current pandemic the continual use of metformin could reduce the mortality rate, from 4 to 1, i.e., a decrease of 75% (as seen in the Wuhan Hospital study previously mentioned) for all risk Covid-19 categories, this would be an exceptional result.

The medical indication for the introduction of the continual use of metformin in the categories most at risk for Covid-19 concerns the people who are over 60 years of age and are obese or overweight, i.e., with a Body Mass Index (BMI) higher than 23.9 for women and 25 for men. The therapeutic dosage is approximately 1.5 grams per day. People taking metformin will also benefit from the side effects of the drug: anti-obesity, anti-aging, anti-cancer, and anti-cognitive decline.

Of course, to lose excess abdominal fat, it is advisable to include a healthy lifestyle and diet, personalized as required, taking into account the conditions of the person and his context in the perspective of the current pandemic. Lifestyle and diet during the Covid-19 pandemic certainly deserve a dedicated study and will be the subject of a future article.

For those over 60 and of normal weight, the proposal, regarding the possible intake of metformin, is to evaluate the individual case from a medical point of view. The possible presence of previously undiagnosed diabetes, prediabetes, and metabolic syndrome (evaluating fasting glycemia, glycated hemoglobin, and insulin) should be considered. A very important parameter to evaluate is the abdominal volume. The simplest thing to do is to measure the waist circumference which, according to the European guidelines, must not exceed the limit of 102 cm in men and 88 cm in women. However, this is an imprecise evaluation because it does not take into account the physical constitution that also concerns the bone mass; thus, using the ratio of the circumference of the waist and that of the hips is much more accurate. Therefore, this ratio should be less than 0.95 for men and 0.8 for women. The amount of lean muscle mass and fat mass and their ratio must also be evaluated as well as whether there is excessive accumulation of intra-abdominal fat.

This evaluation can be performed with bio-impedancemetry. We

may have the case of a normal weight subject in which the ratio between muscle mass and fat mass is unbalanced in favor of fat mass, and the use of metformin, in this case, would favor muscle metabolism compared with that of the adipocyte [64,33].

Metformin, which has already become a therapeutic option against age, obesity, cancer, and cognitive deterioration, would now have, thanks to its metabolic mechanisms, an additional feature as Host-Directed Therapy [65] – therapy aimed at modifying the subject's response to resisting a pathogen – against Covid-19.

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