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REPURPOSING METFORMIN: POTENTIAL AS A PREVENTION, TREATMENT AND ADJUNCT THERAPY IN PANCREATIC CANCER

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Abstract: Metformin, a widely prescribed treatment for type II diabetes, offers promising benefits beyond glycemic control, including improved lipid profiles and cardiovascular outcomes. It inhibits gluconeogenesis in the liver by activating AMPK, thereby reducing glucose production and enhancing glucose uptake in muscle. Recent studies highlight its potential anticancer effects, particularly through the suppression of the mTOR pathway via LKB1-dependent AMPK activation, which inhibits cell proliferation. This review explores metformin's role as an adjunct therapy in pancreatic cancer, summarizing evidence on its molecular mechanisms and potential efficacy. The findings suggest metformin's broader therapeutic applications, especially in oncology, warrant further investigation.

The aim: The aim of this study is to analyze the role of metformin as an adjunct therapy in the treatment of pancreatic cancer, with particular focus on its molecular mechanisms, such as AMPK activation and mTOR pathway inhibition. The study aims to summarize the current scientific evidence regarding its potential effectiveness.

Keywords: metformin, glycemic control, pancreatic cancer, oncology

1. Introduction

Metformin is a dimethylated derivative of biguanides, which, due to its hypoglycemic properties, is commonly used by patients with type II diabetes (T2D) [1]. The drug gained popularity after the publication of the results of the Prospective Diabetes Study (UKPDS), which demonstrated that taking metformin carries greater benefits compared to using insulin and sulfonylurea derivatives. Long-term metabolic benefits and reduced weight gain characterized dimethylbiguanide. Additionally, it reduces the risk of cardiovascular events and hypoglycemic episodes [2]. In the United Kingdom, between 2000 and 2013, there was an increase in the number of prescribed metformin from 55.4% (95% CI 55.0% to 55.8%) in 2000 to 83.6% (95% CI 83.4% to 83.8%) in 2013. It is worth noting that there was also a decrease in the number of prescribed sulfonylurea derivatives from 64.8% (95% CI 64.3% to 65.2%) to 41.4% (95% CI 41.1% to 41.7%) over these 13 years [3].

In individuals with type II diabetes, there is an accelerated rate of gluconeogenesis, which in turn results in high levels of endogenous glucose. Metformin inhibits gluconeogenesis, thereby reducing the amount of glucose produced in the liver [4, 5]. A Swedish research group discovered that a derivative of biguanides enhances muscular glucose uptake [6]. It also contributes to reducing serum triglyceride levels and increasing cholesterol levels in high-density lipoprotein fractions, as demonstrated by researchers from Stanford University School of Medicine [7]. Therefore, one can conclude that the use of metformin positively influences carbohydrate and lipid metabolism. Unfortunately, metformin is not a perfect drug, as its action may result in the occurrence of lactic acidosis, which mostly affects patients with impaired kidney function [8].

The target site of metformin action is the mitochondria, where it inhibits mitochondrial complex I. This leads to a decrease in ATP levels, an increase in AMP levels, and an elevation in the AMP/ATP ratio. Accumulated AMP activates 5'-AMP-activated protein kinase (AMPK), which inhibits gluconeogenesis in the liver. AMPK is an enzyme that plays a crucial role in many biochemical pathways, such as the mammalian target of rapamycin (mTOR) pathway, mitogen-activated protein kinase (MAPK), phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt), Janus kinase/signal transducer and activator of transcription (JAK/STAT), and nuclear factor kappa B (NF-κB) [9, 10, 11]. AMPK phosphorylation also leads to increased glucose transport in muscles and inactivation of acetyl-CoA carboxylase (ACC), an enzyme involved in lipogenesis [12].

The correlation between hyperinsulinemia and the risk of cancer has been scientifically proven. Metabolic syndromes and T2D predispose to carcinogenesis [13]. A meta-analysis conducted

based on information from the Consensus American Association of Clinical Endocrinologists Consensus Conference on Diabetes and Cancer (New York, USA, 2012) showed that the relative risk (RR) of cancer in patients with type 2 diabetes mellitus ranges from 1.1 to 2.5 [14]. As of now, numerous studies have been conducted, and their results indicate the anticancer effects of metformin [15, 16]. Moreover, positive treatment outcomes can be achieved regardless of insulinemia [17].

AMPK-dependent metfomin effects in cancer LKB1-dependent and AMPK-dependent suppression of the mammalian target of rapamycin (mTOR) is one of the strongest anticancer mechanisms of metformin [18, 19]. The LKB1 kinase is the primary activator of AMPK in hepatocytes through its phosphorylation. Reuben J. Shaw and others have demonstrated that the removal of LKB1 from the liver did not disrupt the activation of AMPK in muscles. However, it eliminated the effect of metformin on serum glucose levels [20]. The production of mTOR results from the interaction of two opposing pathways: the Akt (protein kinase B) pathway, which signals nutrient availability, and AMPK, which signals energy depletion. mTOR promotes cell proliferation and growth, including in cancer cells, so its inhibition by metformin leads to disruptions in protein synthesis [21]. Moreover, loss-of-function mutations in the LKB1 gene are responsible for the occurrence of Peutz-Jeghers syndrome, which is a high-risk condition for cancer development [22].

The new application of metformin, a drug popular among diabetics and mainly associated with this disease, as well as the prospect of preventing and treating cancer, prompted us to review the available literature and scientific research. We have created a review focusing on the key aspects and potential of metformin as an adjunct therapy in the treatment of pancreatic cancers.

2. Metformin in Pancreatic Cancer

The incidence of pancreatic cancer (PC) has sharply increased in recent years, and it is estimated to become the second leading cause of death in the USA by 2030 [23]. Despite the high number of cases, effective treatment methods and therapeutic approaches have not been developed so far [24]. The prevailing opinion suggests that the increased incidence of pancreatic cancer is due to the rise in commonly occurring risk factors such as obesity and type 2 diabetes (T2DM) [25]. The number of reported cases of pancreatic cancer associated with type 2 diabetes or defined glucose tolerance disorders hovers around 80% [26]. Pancreatic ductal adenocarcinoma (PDAC) is the most common malignant tumor of the pancreas, and the term "pancreatic cancer" typically refers to this entity [27].

2.1. The risk of Pancreatic Cancer

Since the beginning of the 21st century, numerous scientific studies have been conducted to investigate the relationship between the use of metformin in individuals with type 2 diabetes and the risk of pancreatic cancer. In a five-year clinical-control study conducted at MD Anderson Cancer Center, it was demonstrated that among patients with type 2 diabetes using metformin, the risk of pancreatic cancer was significantly lower compared to patients not taking metformin (OR=0.38; 95% CI=0.22–0.69; P=0.001) [28]. Another meta-analysis from 2013, which reviewed 37 studies involving over 1,500,000 participants, showed a 46% reduction in the risk of developing PDAC among individuals using metformin [29]. Similar conclusions were drawn in a meta-analysis conducted earlier this year. After analyzing 29 studies and creating subgroups, a connection was demonstrated between the use of metformin in individuals with type 2 diabetes and the favorability of this medication (OR=0.82, 95% CI=0.69, 0.98) [30].

2.2. Correlation between taking metformin and the survival of patients with PC

Scientists and researchers are also exploring the correlation between taking metformin and the survival of patients with pancreatic cancer. Sarah J. Skuli and others conducted an analysis comparing results from 21 different studies and demonstrated that the use of metformin was beneficial in the survival of patients suffering from both diabetes and pancreatic cancer, especially in individuals in the early and intermediate stages of the disease. This suggests that metformin may have application as an additional chemotherapeutic drug [31]. Similarly, a retrospective study was conducted at Severance Hospital in Seoul, South Korea, comparing data over more than eight years. It showed that the median overall survival was 13.7 months, while in the group of individuals who did not take metformin, it was 8.9 months (P=0.001). Particularly increased survival was observed in individuals at an advanced stage of the cancer [32]. In a retrospective study conducted at The University of Texas MD Anderson Cancer Center in Houston, a higher 1-year survival rate (63.9% compared to 46.3%), higher 2-year survival rate (30.1% compared to 15.4%), and a longer median overall survival time for all stages of the disease (4.1 months) were observed in favor of metformin use. It is worth emphasizing that a statistically significant difference in survival between patients using metformin and those who did not take this medication was observed only in individuals with non-metastatic disease [33]. The impact of metformin on the survival of patients with pancreatic cancer in various stages was also examined, and conclusions were drawn that this drug improved survival in patients after resection and in patients with locally advanced tumors but not in those with metastatic disease [34]. A systematic review from 2018, which included almost 37,000 patients, showed that adjunctive treatment with metformin improved the survival

of patients undergoing surgical procedures (HR=0.73, 95% CI=0.62-0.870) or comprehensive therapy (HR=0.88, 95% CI=0.79-0.97) and patients with resected or locally advanced tumors. Such improvement was not observed in the group undergoing chemotherapy or in the group with metastatic disease [35]. Further evidence has also shown an improvement in survival among patients with both T2DM and PDAC after pancreaticoduodenectomy. A study conducted at the Asan Medical Center in Seoul, Korea, taking into account the start and end of treatment, demonstrated that the use of metformin was correlated with longer overall survival after surgical intervention. Importantly, this study was adjusted for the bias associated with immortality, which was lacking in many publications and led to incorrect results [36].

In contrast to the previous results, a cohort study conducted in the United Kingdom, involving patients with advanced PAC, showed no significant difference in survival between individuals exposed and those not exposed to metformin in both univariate and multivariate analyses. In both the primary (HR=1.11 [0.89–1.38], P=0.367) and secondary (HR=1.09 [0.80–1.47], P = 0.585) analyses. Neutral effects of metformin were demonstrated [37]. Subsequent cohort studies also did not demonstrate the benefits of using metformin. Roongruedee Ch. and others reported only a 1.0-month longer median survival (9.9 months compared to 8.9) [38].

2.3. Other antidiabetic drugs

The action of metformin has been compared to the use of other antidiabetic drugs. Andrea DeCensi and others found that the use of metformin reduces the risk of developing cancer compared to alternative diabetes treatment methods [39]. In a large, retrospective cohort study conducted in the United Kingdom, it was observed that the use of insulin and insulin-secretagogues correlated with a higher risk of developing solid tumors compared to a lower risk associated with metformin use. Interestingly, a similar relationship was observed both in pancreatic cancer and colorectal cancer [40]. A subsequent meta-analysis from 2017 also demonstrated the favorable effects of metformin on overall survival in patients with pancreatic cancer (HR = 0.77; 95% CI = 0.68–0.87). However, it did not identify benefits associated with the use of other antidiabetic medications, including insulin, sulfonylureas, and thiazolidinediones. It is worth emphasizing that metformin treatment was not significantly associated with progression-free survival (HR=1.22; 95% CI=0.76–1.95) [41]. It has also been demonstrated that the use of insulin or other medications that increase insulin secretion increases the risk of developing PDAC [28].

2.4. Metformin in combination with chemotherapy

Metformin has also been tested in combination with chemotherapy. A randomized clinical trial conducted by Sil Kordes and others did not show an improvement in treatment outcomes after

the introduction of the standard dose of metformin used in diabetes treatment among patients struggling with advanced pancreatic cancer. After 6 months, the overall survival of patients receiving gemcitabine and erlotinib with metformin was 56.7% (95% CI 44.1-69.2), while patients receiving gemcitabine, erlotinib, and placebo had a survival rate of 63.9% (95% CI 51.9-75.9). The obtained result was not satisfactory [42]. Reni M. and others conducted a similar study, but this time they combined metformin with cisplatin, epirubicin, capecitabine, and gemcitabine (PEXG), and applied this treatment to patients with metastatic pancreatic cancer. The 6-month progression-free survival rate was 52% (95% confidence interval (CI), 33–69) in the control group and 42% (95% CI, 24–59) in the metformin group (P = 0.61), which also did not indicate an effective anti-cancer effect of metformin [43]. A compelling result supporting the continued combination of metformin with chemotherapy was shown in prospective studies conducted between 2014 and 2021. Among patients with metastatic PDAC and T2DM treated with insulin and metformin, and receiving gemcitabine and nab-paclitaxel, the median overall survival was 21 months and 33 months, respectively. However, it is worth noting that only 41% of all patients had type 2 diabetes, and 16% were taking metformin [44]. In 2015, metformin was combined with paclitaxel and was used as second-line treatment in patients with pancreatic cancer. This combination also did not extend survival. It is worth noting that the prospective study was conducted in patients with locally advanced or metastatic pancreatic cancer who experienced disease progression during first-line treatment with gemcitabine. Additionally, this combination was poorly tolerated, leading to the discontinuation of further investigations [45]. Rajanna Ajumeera and others, in laboratory conditions, also combined metformin with the microelement pyridoxal phosphate (PLP) and examined the effect of these drugs on the human pancreatic cancer cell line (PANC-1) in in vitro cell culture. PLP clearly induced cell cycle arrest, apoptosis, and increased expression of the p53 protein. However, the combination of PLP with metformin did not lead to synergistic anti-cancer effects [46]. Currently, prospective research NCT04033107 is underway, investigating the combination of high-dose vitamin C with metformin in the treatment of malignant tumors, including pancreatic cancer.

Future studies should include the disease stage, predictive factors, and the level of metformin in cancer cells to comprehensively assess the benefits of metformin in the therapy of PDAC.

3. Conclusions

Metformin shows promising potential in the prevention and treatment of pancreatic cancer, both as an adjunct therapy and, potentially, as a standalone option in the future. Further research is needed to fully understand the mechanisms of metformin's action in oncology and its safety

profile in non-diabetic patients. The current findings are encouraging enough that an increasing number of clinical trials are incorporating metformin as part of treatment protocols for pancreatic cancer patients, particularly those with diabetes. Metformin could become an important component of a multifaceted approach to pancreatic cancer therapy, especially within a personalized medicine framework based on the metabolic and molecular characteristics of the tumor.

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