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Metformin and Physical Activity: Potential Interactions, Molecular Mechanisms and Implications for Lung Cancer Treatment - A Narrative Review

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Abstract
Lung cancer is one of the most common cancers worldwide and the leading cause of cancer-related mortality. Due to altered cellular metabolism in cancer cells, metabolism-modifying agents are increasingly investigated for their potential anticancer effects. Metformin, a biguanide commonly used in the management of type 2 diabetes (T2D), has recently been evaluated as a potential adjunct to standard cancer therapies. Physical activity is also known to influence metabolic pathways involved in cancer progression and may modify treatment outcomes. We conducted a systematic review of the use of metformin in lung cancer treatment.

Publications were retrieved from PubMed, Web of Science, Cochrane, and ClinicalTrials.gov. The results showed that the addition of metformin to cancer therapies demonstrated varying degrees of effectiveness across treatment modalities. Most studies reported improvements in overall survival (OS) and progression-free survival (PFS) when metformin was combined with tyrosine kinase inhibitors (TKIs). Moreover, metformin improved median OS and PFS in most studies evaluating its combination with chemotherapy. The addition of metformin to immunotherapy generally improved OS and PFS, although the results were more variable. Evidence from the literature suggests that both metformin and regular physical activity may exert beneficial metabolic effects relevant to cancer treatment. However, despite promising findings, further clinical studies are needed to clarify their individual and combined impact on outcomes in patients with lung cancer.

Keywords: lung cancer, metformin, cancer treatment, metformin, cancer metabolism, physical activity, cancer therapy

1. Introduction

Lung cancer is the primary cause of cancer fatalities around the world (3). Non-small cell lung carcinoma (NSCLC) accounts for about 80% of all lung cancer cases. Often late diagnosis and an aggressive nature are the cause of the NSCLC unfavourable prognostics (4). Despite significant advancements in diagnosis and treatment, establishing the best treatment to achieve clinical response remains a challenge due to the complexity and variability of the disease in each patient (5). Currently new approaches to the NSCLC treatment are examined, with great focus on the targeted therapies. Promising results are expected from the metabolism altering drugs (6, 7). Considering their mechanism of action based on aiming at the dysregulated metabolic functions of the cancer cells, they may target the cells otherwise resistant to the other forms of treatment (6, 8). The possibly targetable mechanisms of the cancer cells metabolism can be represented by glucose metabolism due to its crucial role in cell function (7, 8). Antidiabetic drugs became the most well-documented metabolic medicaments researched in cancer treatment, overrepresented by the metformin (8).

Metformin (1,1-dimethylbiguanide hydrochloride) is a biguanide commonly used in the type 2 diabetes (T2D) management. The drug enhances glucose tolerance in patients, reduces both baseline and after-meal blood glucose levels. Metformin achieves this by reducing hepatic glucose production, decreasing the absorption of glucose in the intestines, and enhancing insulin sensitivity through the promotion of peripheral glucose uptake and utilization. Due to its effectiveness in lowering blood sugar and its favorable safety profile, metformin stands as one of the most commonly prescribed antidiabetic medications, maintaining its position as the primary treatment for T2D (1,2).

Physical activity is increasingly recognized as an important factor influencing cancer prevention, treatment outcomes, and quality of life in patients with malignancies. Regular exercise has been shown to improve insulin sensitivity, reduce systemic inflammation, enhance immune function, and modulate cellular energy metabolism through pathways that partially overlap with those affected by metformin, including AMP-activated protein kinase (AMPK) signaling. In patients with lung cancer, physical activity may contribute to improved functional capacity, reduced treatment-related fatigue, and better overall prognosis. Therefore, the potential interactions between metformin therapy and physical activity warrant further investigation. (70-72)

Multitude of studies investigated the propable anticancer mechanisms of metformin in vitro and in vivo studies (9-23). The possible effects of this biguanide include disregulation of the turmogenic processes, tumor angiogenesis, infiltration, and cancer cell migration(10-23). Although the results obtained in preclinical studies deem metformin very promising as possible anticancer agent, there is an distinct lack of the clinical trials veryfing this findings on the large scale, as the clinical research on the anti-tumor effect of the biguanide remains sparse.

In the light of recent findings we decided to evaluate the potential role of the metformin in NSCLC anticancer therapy. We retrieved preclinical and clinical trials investigating anticancer mechanism of the metformin in the cancer cell lines, xenographs and patients diagnosed with NSCLC treated with various anticancer agents and metformin.

2. Molecular mechanism of action of the metformin with different anti cancer agents

Metformin demonstrates a vast array of the antitumor effects, including cancer cell apaptosis stimulation, antiproliferative and antivascular effect, impairment of the invasion and the migration process and supression of the tumor growth. The specific mechanism of the

antitumorigenic actions/functions of the metformin are intricate and not completely discovered. To the most prominent and well investigated belongs the process of AMPK activation, which can occur in multiple pathways.

Metformin's influence on the LKB1-AMPK kinase pathway can lead to the tumor growth inhibition (10). The downstream target of this pathway is the mammalian target of rapamycin (mTOR), a crucial point of the metformin action in tumor suppression. mTOR serves as the catalytic subunit of mTOR complexes 1 and 2 (mTORC1 and mTORC2), regulates cell growth and integrates signals from hormonal and energy-sensing pathways, including insulin, insulin-like growth factor 1 (IGF-1), IGF-2, and AMPK (11,12).

AMPK activation triggers the formation of the tumor-inhibitory complex involving tumor suppressor genes TSC1 and TSC2/ mTORC1, leading to mTORC1 downregulation – this mechanism causes the blockage of protein synthesis and cancer cell proliferation. Furthermore metformin-induced AMPK activation mediates other anticancer mechanisms, including growth differentiation factor 15 (GDF15) increased expression and regulated EMT- and migration-related protein expression, important factors in cancer cell migration and invasion (24).

Metformin exhibits the ability to inhibit mTOR and impede cell cycle progression by acting through AMPK activation, regulation in DNA damage and development 1 (REDD1)(12, 13). Moreover, AMPK activation by metformin can stimulate the expression of the endoribonuclease DICER, an enzyme involved in microRNA (miRNA/miR) synthesis. Alterations and loss of function in DICER are associated with complex tumor syndromes, suggesting that metformin-induced DICER expression might contribute to its antitumor effects (15). Furthermore metformin inhibits the proto-oncogene c-Myc and hypoxia-inducible factor 1α (HIF-1α) through AMPK, adding to its multifaceted impact on tumor-related pathways, including diminishing radioresistance of the cancer cells (25). Downregulation of insulin like growth factor 1 (IGF-1), a process achieved through the inhibition of the PI3K/AKT and MEK/ ERK signaling pathways in lung cancer cells is triggered by metformin. This regulatory action on lung cancer cell metabolism and proliferation is well-documented (16). In NSCLC, the activation of the PI3K/AKT/mTOR signaling pathway is associated with a more aggressive form and a poorer prognosis, particularly in squamous cell carcinoma. Metformin intervenes in this pathway by obstructing the IGF-1-insulin signaling route, ultimately preventing mTOR activation and inhibiting lung cancer cell growth (17). Moreover, metformin induces apoptosis through the MAPK signaling pathway and upregulation of growth arrest and DNA damage-

inducible 153 (GADD153). Metformin induces cell cycle arrest in lung cancer cells through the MAPK signal transduction pathway, showcasing its anti-proliferative and pro-apoptotic effects in the context of the lung cancer (18).

Metformin is also associated with repealing the EGFR-TKI resistance by restoring the sensitivity of the EGFR-TKI-resistant cells to EGFR-TKI by inhibition of the IGF-1R (by siRNA) pathway, expression of IGFBP3, down-regulation AKT and enhancement of the BIM-mediated synergistic antitumor effects. IGF-1R inhibitors, such as α-IR3, AG-1024, or R1507 interact with EGFR-TKI to enhance TKI induced cell growth inhibition and apoptosis (13-23). Additionally metformin has been found to enhance the tumor apaptosis process in combination with different medicaments including cisplatin, atorvastatin and buparlisib. The dose-dependent antiproliferative propreties of the metformin evaluaved among others on the A549 cell lines acted synergistically with other anticancer drugs in various possible mechanisms, including Akt/FoxO3a/Puma axis, alterations in MAPK and AMPK and sensitization of the tumor cells to the cisplatin-induced apoptosis through the key NER factors, XPA, ERCC1 and XPF (25, 26, 27).

3. Metformin in the human studies

Metformin remains a promising concurrent medicament in the cancer treatment, mainly improving the survival of the patients with diabetes mellitus and higher BMI scores. In patients with early stage NSCLC (stage I and II) multivariate analysis metformin was found to significantly improve PFS in comparison with nonmetformin ($P = .057$) and not-diabetic ($P = .017$) groups, although the association between dose and PFS was not significant ($P = .703$)(28). Patients using metformin with an ordinal discretized BMI showed a higher survival rate than other groups ($P < .001$) Metformin administration with high BMI (BMI $\geq$25) and previous smoking status presented improved survival compared with all other categories, with patients with BMI 30 to <35 having the highest increased survival rate (29). Exposure to metformin was associated with a significantly lower risk of death (HR 0.82, 95% CI 0.73–0.92) and lower risk of lung cancer-specific mortality approaching statistical significance (HR 0.82, 95% CI 0.72–92) in diabetic patients. The cumulative metformin dose did not influence both lung cancer-specific and overall mortality (30).

4. Influence of Physical Activity on the Effectiveness of Metformin

Physical activity and metformin are among the most widely recommended interventions for improving metabolic health and preventing the progression of metabolic disorders. Both strategies have been shown to improve insulin sensitivity, glucose utilization, and overall metabolic homeostasis. Importantly, exercise and metformin influence several overlapping molecular pathways, including AMP-activated protein kinase (AMPK) signaling, mitochondrial biogenesis, glucose transporter type 4 (GLUT4) translocation, and cellular energy metabolism. Due to these similarities, researchers have become increasingly interested in understanding whether the simultaneous use of metformin and exercise results in additive benefits or whether pharmacological treatment may alter exercise-induced physiological adaptations [70].

Exercise training is recognized as one of the most effective non-pharmacological interventions for improving cardiometabolic health. Regular aerobic and resistance exercise enhances skeletal muscle glucose uptake, increases mitochondrial density, improves endothelial function, reduces systemic inflammation, and contributes to favorable body composition changes. Many of these adaptations are mediated through AMPK activation and subsequent stimulation of mitochondrial biogenesis. Interestingly, metformin also activates AMPK-dependent pathways, leading to the hypothesis that combining exercise with metformin could amplify beneficial metabolic responses. However, growing evidence suggests that the interaction between these interventions is more complex than initially anticipated [70].

One of the most influential studies investigating this issue was conducted by Konopka et al. In this randomized controlled trial involving older adults, participants completed a structured aerobic exercise training program while receiving either metformin or placebo. Although both groups experienced improvements in metabolic health, individuals treated with metformin demonstrated significantly smaller increases in maximal oxygen consumption (VO_2max), a key indicator of cardiorespiratory fitness. Furthermore, metformin-treated participants exhibited attenuated improvements in insulin sensitivity and reduced mitochondrial adaptations within skeletal muscle tissue. The authors suggested that metformin may interfere with exercise-induced mitochondrial remodeling, thereby limiting some of the beneficial physiological responses typically observed following endurance training [70].

Similar findings have been reported in studies evaluating resistance exercises. The MASTERS trial, conducted by Walton et al., examined the effects of metformin during

progressive resistance training in older adults. Resistance exercise is known to stimulate muscle protein synthesis and promote skeletal muscle hypertrophy, which are essential adaptations for maintaining physical function and metabolic health during aging. However, participants receiving metformin experienced significantly smaller increases in lean body mass and muscle fiber cross-sectional areas compared with individuals assigned to resistance training alone. These results indicate that metformin may partially blunt anabolic responses to resistance exercise and reduce the extent of muscle growth induced by training [71].

The interaction between exercise and metformin has also been investigated in individuals with impaired glucose regulation. Malin et al. evaluated the independent and combined effects of exercise training and metformin treatment in subjects with prediabetes. Both interventions improved insulin sensitivity and glycemic control when applied separately. Surprisingly, the combination of exercise and metformin did not result in greater metabolic benefits than exercise alone. In some measured outcomes, the magnitude of improvement appeared lower in the combined intervention group than in participants performing exercise without pharmacological treatment. These findings suggest that metformin may attenuate some of the beneficial metabolic adaptations induced by physical activity, particularly those associated with improvements in insulin action [72].

Recent evidence has further strengthened this hypothesis. Azócar-Gallardo et al. investigated the effects of a concurrent training program performed with or without metformin treatment. Participants undergoing exercise training demonstrated significant improvements in cardiorespiratory fitness, body composition, and metabolic markers. Although metformin independently exerted favorable metabolic effects, the combination of exercise and metformin did not consistently outperform exercise alone. Moreover, some indicators of aerobic performance improved to a lesser extent in individuals receiving metformin concurrently with training. These observations support the concept that metformin may partially interfere with exercise-induced physiological adaptations despite its recognized therapeutic benefits in metabolic disease management [73].

Several biological mechanisms have been proposed to explain these findings. Exercise-induced adaptations depend largely on transient increases in cellular stress and reactive oxygen species production, which stimulate mitochondrial biogenesis and activate signaling pathways involved in muscle remodeling. Metformin has been shown to alter mitochondrial complex I activity and cellular energy metabolism. Although these effects contribute to improved

glycemic control, they may simultaneously reduce the metabolic signals required for optimal exercise adaptation. Consequently, the beneficial stress response generated during physical activity may be attenuated in individuals receiving metformin treatment [70,71].

Another important consideration is the population being studied. Most available investigations have been conducted in older adults, overweight individuals, or patients with prediabetes. Therefore, it remains uncertain whether similar interactions occur in younger healthy individuals, competitive athletes, or patients with cancer. Nevertheless, current evidence consistently suggests that regular physical activity alone produces substantial improvements in metabolic health and physical performance, while the addition of metformin does not necessarily enhance these benefits and may even reduce selected training adaptations [70-73]. From a clinical perspective, these findings should not be interpreted as evidence against metformin therapy. Metformin remains one of the most effective and extensively studied pharmacological treatments for insulin resistance and type 2 diabetes mellitus. However, the available literature indicates that clinicians should consider the potential interaction between metformin and exercise when designing lifestyle and pharmacological interventions. In physically active individuals, particularly those aiming to maximize improvements in aerobic capacity or muscle hypertrophy, the metabolic benefits of metformin may not translate into superior exercise-related outcomes [70-73].

Overall, current evidence suggests that physically active individuals achieve considerable metabolic and physiological benefits from exercise alone. While metformin provides well-established therapeutic effects in metabolic disorders, its concurrent use with structured exercise programs does not appear to produce synergistic improvements and may attenuate selected adaptations related to mitochondrial function, cardiorespiratory fitness, insulin sensitivity, and skeletal muscle growth. Further large-scale randomized clinical trials are necessary to determine the clinical significance of these interactions and to identify patient populations that may benefit most from combined exercise and metformin interventions [70–73](Figure 1).

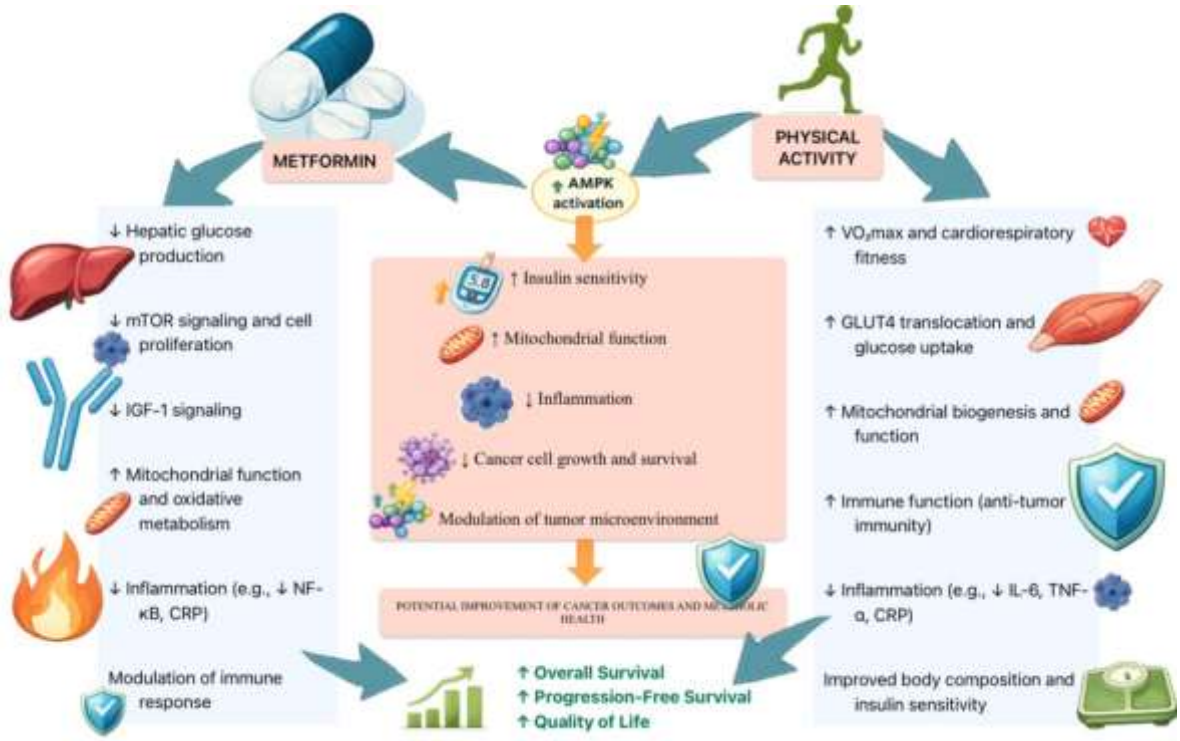

Figure 1. Shared metabolic and physiological pathways influenced by metformin and physical activity. Metformin and physical activity affect several overlapping mechanisms, including AMPK activation, insulin sensitivity, mitochondrial function, glucose metabolism, inflammation, and immune regulation. These pathways may contribute to improved metabolic health and potentially better clinical outcomes in patients with lung cancer.

Source: Own elaboration based on references 1, 2, 10–18, 24, 57, 70–73 and Sections 2 ("Molecular mechanism of action of the metformin with different anti-cancer agents"), 4 ("Influence of Physical Activity on the Effectiveness of Metformin"), and 7 ("Discussion").

5. Metformin in preclinical studies in lung cancer treatment

5.1 . Potential role of the metformin in the tyrozine kinase inhibitor (TKI) therapy in the lung cancer

Majority reserach on the role of metformin in tyrozine kinase inhibitors was conducted on the application of EGFR-TKI medicaments. All TKI therapeutics investigated in the studies represented EGFR-TKIs, including erlotinib, afatinib, gefitinib, osimertinib or were not specified. Most studies reported substantial improvements in both OS and PFS (median 29.8 and 17.4 months, respectivelly) with metformin. Su et al did not find any significant differences in time to treatment failure indepently of the metformin administraion status. In majority of the studies NSCLC subtype was not further specified, meanwhile Arietta et al investigated adenocarcinoma patients only (31, 32). Arietta et al. noted that patients assigned to receive a

combination of EGFR-TKIs and metformin exhibited a higher likelihood of responding positively to EGFR-TKIs therapy (71% [49/69] vs 54% [38/70]) (31). In Han et al. Study the addition of metformin resulted in a notably higher ORR which were respectively 85.7% and 47.4%. Further examination indicated that metformin significantly extended the median PFS2 during osimertinib therapy among individuals who experienced progression following prior EGFR-TKI treatment due to the secondary EGFR T790M mutation, suggesting that simultaneous use of the metformin might also offer advantages to EGFR-mutant NSCLC patients (32). Patients with NSCLC and type II diabetes mellitus were found to significantly benefit from the combined treatment (9,2 vs 6,4 months PFS and 33,4 vs 25,4 months OS) (33). Similarly addition of the metformin in patients with a BMI of 24 or higher was independently associated with a prolonged OS (HR, 0.55; 95% CI, 0.31-0.98; P = .04) and PFS (hazard ratio [HR]: 0.47 [95% CI, 0.28-0.78]; P = .003). Patients with BMI of 24 and higher, who received metformin presented an improved PFS and OS compared to those who received EGFR-TKIs alone, with PFS durations of 15.83 months and 8.34 months and OS durations of 31.44 months and 18 months, respectively. Contrarily, this enhancement was not observed in patients with a BMI lower than 24 (n = 63) (34). Other hypoglycemic agents were found less effective than metformin in combination with EGFR-TKI treatment, achieving worse PFS (9 months vs 19 months) and OS (23 months vs 32 months)(35). Li et al study observed non-significantly worsened outcomes in the non-diabetic patients treated with metformin with lowered median PFS (10.3 months vs. 11.4 months) and median OS (22.0 months vs. 27.5 months). Although ORRs were comparable between the two treatment arms (66% vs. 66.7%), metformin addition to the TKI treatment in non-diabetic patients was linked with the increased toxicity in form of remarkably higher incidence of diarrhea (36).

5.2. Potential role of the metformin in the chemotherapy of the lung cancer

Metformin consistently improved effectiveness of the chemoterapy and chemoradiation treatment in diabetic patients with median OS and PFS of 18 and 8.8 (5) months, respectivelly (37, 38, 39). Wang et al established that the metformin user group had a better prognosis and improved survival outcome ($p<0.001$) and better adjusted hazard ratio of overall survival (aHR=0.61, $p<0.001$) compared with the non-metformin user group. In Pietras et. Al,Wen-Xiu et al and Ahmed et al the addition of metformin to chemotherapy or chemoradiation in diabetic patients did not show any statistically significant improvement in ORR, PFS and OS (40).

Across studies patients were treated mainly with chemotherapy consisting of cisplatin or carboplatin, oftentimes in combination with docetaxel, gemcitabine or etoposide (37-39, 41-43). The daily dose of metformin varied between 500mg-2000mg, with 500mg or 1000mg administered twice or thirce daily (38, 41-45). In the Wang et al study the adjusted HR of the metformin user subgroups varied between the prescribed daily dose of the medicament. For the <1500 mg subgroup aHR amounted for 0.52 ($p < 0.001$), and for the dose of 1500mg and more aHR was 0.42 ($p < 0.001$). The chemoradiation in combination with metfromin in non diabetic patients was disadvantegous and worsened the outcomes (44, 45). In Skinner et al research addition of the metformin did not improve survival among non-diabetic patients with unresectable stage III NSCLC with one-year PFS rates and OS rates accounting for 60.4% and 80.2% for control group and 51.3% and 80.8% in the metformin group respectively (45). Similarly the inclusion of metformin into the chemoradiotherapy treatment resulted in diminished treatment effectiveness with one year PFS and OS lower in metformin group than in control patients (34.8% vs 63.0% and 47.4%; vs 85.2%) and elevated adverse effects when compared to the efficacy and side effects of combined modality therapy alone in Tskaridis et al study (44). Chemoradiation was composed of simultanous platnium based chemotherapy and radiation in fraction doses between 1.5–2.75 Gy to total dose of 60 Gy (50-63Gy)(37, 44, 45). The impact of metformin on the recurrence-free survival (LRFS) and distant metastasis-free survival (DMFS) was examined on patients undergoing chemoradiotherapy treatment. In patients with diabetes mellutis the control group exhibited a median overall LRFS of 44 months, while this endpoint was not reached for the metformin group. The two-year DMFS was significantly higher for the metformin group (74% versus 53%), as well as PFS (58% versus 37%) and OS (62% versus 49%). The use of metformin was a statistically significant independent variable for DMFS and PFS ($p = 0.02$ and $p = 0.03$, respectively) (37). In non-diabetic patients treated with chemoradiation with or without meformin recurrence-free survival (LRFS) and distant metastasis-free survival (DMFS) were similar between the studys arms (45).

The effects of chemotherapy plus metformin regime in non-diabetic and mixed cohorts remained unconclusive, with contradictory results of the studies. No significant contrast observed in the risk of disease progression and mortality between the metformin group and the control group was observed in 164 patients with chemo-native, EGFR-ALK wild-type, stage IIIB/ IV NSCLC, out of whom 36 were diabetic and randomly assigned to both groups (43).

According to Sayad et al addition of the metformin was found to non-significantly improve objective response rate (ORR) of 46.7% versus 13.3% (p=0.109) and OS of 12 months versus 6.5 months (p=0.119)in meformin-naive, non-diabetic group and to lessen the experienced nausea with 26.7% versus 66.7% patients reporting this ailment (41). Maronne et al noted the significant benefit of the metformin treatment in non-diabetic patients with median PFS of 9.6 months in comparison to 6.7 months in control arm (p = .024) (41). The difference in median OS between groups (15.9 months vs 13.9 months) was not statistically significant (p = .186) (42). In Lee et al study patients with squamous cell carcinoma (SqCC) had higher fluorodeoxyglucose (FDG) uptake than non SqCC NSCLC ones and presented significantly decrease the risk of progression and death with the addition of metformin independly of the diabetes status. It was also found that the patients receiving metformin had higher HDL-cholesterol level compared to control group (43).

Metformin compared to other diabetic medications was associated with significantly better survival and enhanced disease control (39, 46). Combining results of groups with addition of insulin and other medications excluding metformin and insulin (10) suggested an inclination for the enhanced disease control in metformin group when compared to the non-metformin groups (39). Diabetic patients with NSCLC receiving metformin were also found to be less likely to have a tumor relapse (38). Chemoradiotherapy and metformin treatments were associated with increases in GDF15 levels during treatment in Di Pastena et al study, although the changes in GDF15 were not identified as prognostic for outcomes (47).

5.3. Potential role of the metformin in the immunotherapy of the lung cancer

Several studies investigated metformin as a concomitant during the ICI treatment, either alone or coadministered with other medications, antidiabetic or otherwise, as statins and beta-blockers. Although several studies suggest the clinical advantage of metformin usage in the course of the ICI treatment, a few have reached statistical significance (40, 48-52). In multiple studies no influence of metformin on the PFS and OS or ORR has been found(48,49, 53-55).

A statistically signicifant improvement of the ORR and disease control rate (DCR) in metformin treated patients was found by Pietras (ORR 25% vs 13%; p= 0.038) and Yang (ORR 24.7% vs 14.8%, p = 0.025). Jacobi (ORR 39.7 vs. 20.0%, p = 0.38; DCR 40.5 vs. 35.0%, p = 0.61) and Afzal (ORR 41.1% vs 30%, p = 0.4; DCR 70.6% vs 61.6%, p = 0.5) findings regarding ORR and DCR increase did not reach the statistical significance (40,48,49). Jacobi

et al found the metformin advantageous in diabetic patients, however non-diabetic patients achieved higher ORR and DCR (48). Randall et al assosciated the administration of the metformin with better PFS only in overweight patients on immunotherapy ($p = 0.024$).

In Yang and Afzal studies diabetic patients receiving metformin experienced greater advantage in ORR, OS and PFS than the non-diabetic cohort. Afzal studies suggest that the duration of concurrent metformin and ICI therapy had significant impact on OS [($p = 0.01$) and ($p = 0.009$), respectively] and the duration of concurrent metformin and ICI therapy had a statistically significant impact on PFS [($p = 0.03$) and ($p = 0.002$), respectively]. The immune related adverse effect rate in Yangs et al study was slighlty higher in the meformin group, although it did not reach the statistical significance. Additionaly, addition of the DPP4 inhibitors was found not to improve PFS, as compared with metforminalone with ICI treatment (PFS: 7.1 months with metformin alone vs. 4.9 months with metformin and DPP4 inhibitor; $p = 0.513$).

Wang et al established metformin use as an independent favorable prognostic factor for the patients with lung cancer. Metformin use was identified as independent predictive factors for the PFS ($p = 0.013$) and OS ($p = 0.026$). and significant prognostic factor ($p = 0.016$) of lung cancer patients in the multivariate analysis (50) [h]. Five target genes of metformin, including RPS6KA5, RORA, SH3BP5, NUPR1, and CD40LG were identified in treated patients and were expressed increasingly in immune cells, such as CD4+ T cells, CD8+ T cells, natural killer cells, monocytes or macrophages, B cells and Treg cells. This confirmed their prognostic role as a favourbale factor and indicated immune infiltration of the tumor (50).

In Cortellini et al research administration of metfromin was assosciated with increased risk of death (HR, 1.35; 95% CI,1.09–1.66) and disease progression/death (HR, 1.23; 95% CI,1.02–1.49), although the patients receiving metformin were more likely to be older, male, have a higher BMI,a higher burden of metastatic sites and with a higher proportion of NSCLC, what could have influenced the results (56).

6. Materials and methods

This study was designed as a systematic review evaluating the molecular mechanisms of action and the preclinical and clinical effectiveness of metformin in lung cancer treatment. The review focused on studies assessing metformin as a single metabolic modulator or as a concomitant

agent used with anticancer therapies in lung cancer, particularly non-small cell lung cancer (NSCLC).

6.1 Literature search strategy

A systematic literature search was conducted in the following electronic databases: PubMed, Web of Science, the Cochrane Library, and ClinicalTrials.gov. The search was performed to identify publications investigating the role of metformin in lung cancer treatment, including both mechanistic and therapeutic studies.

6.2 Eligibility criteria

Studies were considered eligible if they evaluated the anticancer role of metformin in lung cancer models or in patients with lung cancer. Both preclinical and clinical studies were included. Preclinical studies comprised in vitro and in vivo investigations, including experiments performed on lung cancer cell lines and xenograft models. Clinical studies included studies conducted in patients diagnosed with NSCLC who received metformin alone or in combination with anticancer treatment modalities such as tyrosine kinase inhibitors (TKIs), chemotherapy, chemoradiotherapy, or immunotherapy. Publications were excluded if they did not concern lung cancer, did not assess metformin-related effects, or did not provide data relevant to the molecular mechanisms or treatment outcomes of interest.

6.3 Study selection

Retrieved records were screened for relevance on the basis of title, abstract, and full-text assessment. Studies meeting the eligibility criteria were included in the final qualitative synthesis. The selection process aimed to identify studies addressing both the biological mechanisms of metformin and its potential clinical utility in lung cancer treatment.

6.4 Data extraction

Data were extracted from the eligible studies regarding study design, study population or experimental model, type of anticancer treatment, metformin exposure, and reported outcomes. For preclinical studies, particular attention was paid to the molecular pathways associated with metformin activity, including AMPK, mTOR, PI3K/AKT, MAPK, IGF-1-related signaling, epithelial-mesenchymal transition, apoptosis, proliferation, migration, and treatment resistance.

For clinical studies, extracted outcomes included overall survival (OS), progression-free survival (PFS), objective response rate (ORR), disease control rate (DCR), recurrence-related outcomes, and adverse events when available.

6.5 Data synthesis

The included studies were analyzed qualitatively. The findings were grouped according to the main area of investigation: molecular mechanisms of metformin action, preclinical evidence, and clinical outcomes. Clinical evidence was further organized according to treatment modality, including EGFR-TKI-based therapy, chemotherapy or chemoradiotherapy, and immunotherapy. Due to the heterogeneity of study designs, patient populations, interventions, and reported endpoints, a narrative synthesis was performed instead of a quantitative meta-analysis.

6.6 Outcome measures

The main outcomes of interest were the anticancer mechanisms of metformin and its impact on treatment efficacy in lung cancer. In clinical studies, the principal endpoints included OS and PFS, while secondary outcomes included ORR, DCR, recurrence-related measures, and toxicity profiles. In preclinical studies, the main outcomes included effects on cell proliferation, apoptosis, migration, invasion, signaling pathways, and treatment sensitization.

6.7 Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author

7. Discussion

Metformin is a commonly used anti-diabetic drug, that might also present an antitumor effect by its action on several signaling pathways, such as insulin-indirect and activation of LKB1-AMPK direct, leading to the inhibition of the tumor growth. Moreover, metformin has an impact on the corresponding targets, such as mTORC, PI3K, K-RAS, c-Myc, HIF-1alfa, PP2A and miRNA (10-18).

Moreover, metformin can reduce the immune exhaustion of CD8+ lymphocytes, enhancing the immune response against tumors. Therefore, incorporating metformin could be

a beneficial approach in overcoming acquired resistance to immune checkpoint inhibitors. Li et al.'s preclinical research revealed metformin's ability to reverse resistance to EGFR-TKIs by reversing EMT and inhibiting the IL-6 signaling pathway (57). Another recent study showed that combining metformin with gefitinib could overcome primary resistance to gefitinib by targeting the IGF-1R signaling pathway (19). Several retrospective studies have also suggested that metformin may enhance survival in lung cancer patients treated with EGFR-TKIs (58).

Lee et. Al study suggests that metformin shows a combined anti-cancer effect in tumors that depend greatly on the glucose metabolism (43). Moreover, the effectiveness of the metformin might be related to patients' BMI. According to Arrieta et. Al, patients that recevied EGFR-TKIs combined with metformin with BMI over 24 experienced an improvement in PFS compared to patients that were treated only with EGFR-TKIs and ones with BMI under 24 (34). It was also found out that metformin, compared to other hypoglycemic agents, gave better results when added to the threapy (35, 39, 46). Moreover, metformin addition elongated the median PFS among patients with the progression of the disease while on osimertinib due to the EGFR T790M mutation (32).

The addition of the metformin for EGFR-TKI treated patients was associated with a better outcome among all the diabetic patients, compared to non-diabetic patients not receiving metformin (32-34), In case of non-diabetic patients receiving metformin in combination with EGFR-TKI therapy, the only two papers presented mixed results, which suggests a need for further research (31,36).

Various studies have yielded mixed results regarding the efficacy of combining metformin with chemotherapy. When reviewing research involving cancer patients with any form of diabetes, the findings appear encouraging. The inclusion of the metformin was observed to prolong one-year PFS as well as OS (39, 42, 46). Furthermore, metformin demonstrated superior efficacy compared to the alternative medications utilized in the management of the diabetes concerning the aforementioned outcomes (39).

Nevertheless, among patients without a history of diabetes, metformin was discovered to exacerbate the treatment outcomes by reducing the median PFS among individuals in the cohort receiving metformin supplementation (36, 45). Furthermore, the OS rate was noted to decrease with the simultaneous administration of this antihyperglycemic agent (44). Meanwhile, other studies suggested beneficial effects of the metformin addition to the EGFR-TKI and chemotherapy treatment for non-diabetic patients. Although results as median OS,

two-year OS, PFS or ORR were improved in patients receiving this drug, they mostly did not reach the treshold of statistical significance (31, 36, 41, 42). It is formidable to evaluate its effectiveness when the studies are so contradictory.

Influence of the metformin on the immune checkpoint inhibitor therapy remains vague and disputable. In majorty of studies metformin was found to either positively impact the effects of immunotherapy treatment in patients with NSCLC with diabetes or steroid-induced hyperglycemia (40) or not to effect the course of treatment. To our knowledge, the usage of the metformin in the non-diabetic inviduals has not been yet investigated, although the present literature suggests that the advantage of the metformin in the ICI treatment steems rather from the better glycemic control in diabetic patients than from the direct anticancer influence of the biguanide. Multiple studies indicate that the poorer glycemic control and unregulated diabetes are the factors responsible for the poorer response, shortened OS and PFS and worse prognosis.

Nonetheless, based on few studies it can be stated that metformin does not have a negative impact on overall treatment (40, 49), and even brings slight benefits (40). Moreover, metformin can facilitate overcoming resistance to the ICI therapy – in Kim et al. Study addition of metformin to nivolumab monotherapy halted the disease's advancement for more than 6 months without side effects (59). Similary, Viveiros et. Al presented a case report of a 75 year-old patient, that experienced progression of the disease on nivolumab therapy. The combination of nivolumab and metformin induced a new response, better toleration to the treatment and a stabilization of the disease for 17 months (60).

The reduction of risk of lung cancer in the course of metformin administration remains inconclusive, similarly as the role of the glycemic control in the lung cancer incidence in diabetic patients (61-67). Nonetheless, metformin was reported to reduce the risk of metastatic disease related with occurrence of lung malignancy (61-63). On the contrary, better glycemic control was found to decrease risk of death and result in survival benefit (68). In multiple studies the best glycemic control was obtained by administration of metformin in comparison with different antidiabetic medications as sulfonylureas or insulin without metformin coadministration (69). The ambiguous results suggest the further need for more precise research, possibly on bigger and more specified research groups, notably in non-diabetic patients.

An important aspect that should be considered when evaluating the effectiveness of metformin is the patient's level of physical activity. Both exercise and metformin influence

energy metabolism, insulin sensitivity, mitochondrial function, and AMPK signaling pathways, suggesting potential interactions between these interventions. Regular physical activity is recognized as an important component of supportive cancer care and has been associated with improved functional capacity, reduced fatigue, enhanced quality of life, and better metabolic control in cancer patients. However, recent evidence indicates that the interaction between metformin and exercise may be complex. Konopka et al. demonstrated that metformin attenuated mitochondrial adaptations normally induced by aerobic exercise training in older adults (70). Similarly, Walton et al. reported that metformin blunted gains in muscle hypertrophy during progressive resistance training, suggesting that the drug may partially interfere with certain exercise-induced physiological adaptations (71). On the other hand, Malin et al. found that both exercise and metformin independently improved insulin sensitivity in individuals with prediabetes, although the combined intervention did not always produce additive benefits (72). More recently, Azócar-Gallardo et al. demonstrated that concurrent exercise training combined with metformin treatment improved several metabolic markers and cardiorespiratory fitness parameters, indicating that the interaction may depend on the studied population and measured outcomes (73).

These findings may be particularly relevant in patients with lung cancer, who frequently experience reduced exercise capacity, cancer-related fatigue, and metabolic disturbances. Although no clinical studies included in the present review directly compared the effectiveness of metformin between physically active and sedentary patients with NSCLC, it is plausible that physical activity may modify the therapeutic response to metformin through shared metabolic pathways. Future oncological studies should therefore incorporate assessments of physical activity levels and exercise interventions to determine whether the anticancer effects of metformin differ between active and sedentary individuals and whether combined lifestyle-pharmacological approaches can improve clinical outcomes.

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