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Study on the physiological respiratory changes in patients on metformin therapy

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Abstract
Introduction: The following study has discussed how metformin is employed for different types of diabetes as an "antidiabetic therapy". It explains how chronic hyperglycemia damages organs, and how metformin helps reduce glucose levels by decreasing absorption and enhancing insulin sensitivity. The study also mentions the importance of HbA1c and fasting plasma glucose for measuring glycemic control.
Aims and Objectives: To evaluate the changes in respiratory physiology in patients receiving metformin therapy.
Methods: To conduct this research, the researcher used ANOVA statistical software. By implementing this statistical software, the researcher was able to properly compare % between different groups through Chi-square, the student's t-test, with the similar average scores. This research was completed among adults who were the age groups from 18-75 as well as suffered with Insufficient Glucose Tolerance (IGT), severe COPD, BMI >25, kg/m^2, and nutrition type 2 diabetic mellitus (T2DM).
Result: Through this study, the researcher used different kinds of statistical data, ANOVA statistical software, and tables to complete this research. Again, this study has been approved by the hospital's ethical review board. Furthermore, this research included individuals in the age group from 18 to 75 who were obese with COPD symptoms. On the other hand, the clinical trial showed the effectiveness of metformin in reducing fasting plasma glucose levels.
Conclusion: Metformin was an effective antidiabetic therapy with potential benefits for COPD. It Combined with GLP-1R agonists improves airway inflammation and bronchoconstriction. Metformin was well-tolerated with no significant adverse effects.

Keywords: Antidiabetic, physiological respiratory, metformin therapy, glucose, diabetes

Introduction

A significant consequence of diabetes mellitus is the burden associated with the disease as well as disability caused due to damage the end organ. Chronic hyperglycaemia leads to damage to connective tissues as well as blood vessels. DM adversely affects the normal functioning of the respiratory system. Metformin is currently established as "antidiabetic therapy" for the treatment of diabetes type 2 among patients. Metformin is utilized for treating high blood sugar caused due to diabetes mellitus [1]. In the case of this particular diabetes either cells fail to produce enough insulin or the insulin produced is less effective. Metformin is used along with sulfonylurea, an antidiabetic medicine, or in combination with insulin for reducing sugar levels in the blood. Metformin therapy diminishes glucose absorbed from food and it also enhances the response of the body to insulin. However, metformin is not used in the treatment of diabetes type 1.

Insulin is responsible for maintaining blood glucose concentration. Type 2 diabetes occurs due to decreased sensitivity to insulin, resulting in enhanced glucose concentration in the blood. The Pharmacodynamics aspects of metformin highlight that it reduces glucose production in hepatic cells, decreasing absorption of glucose by the intestine and increasing insulin sensitivity through enhancing glucose uptake. In contrast with the administration of sulfonylurea, insulin secretion remains unchanged with metformin usage. HbA1c is crucial for measuring glycaemic control that is used for monitoring diabetic patients. "Fasting plasma glucose" is useful for measuring glycaemic regulation.

In 29 weeks of a clinical trial, individuals diagnosed with "type II diabetes" metformin resulted in a reduction of fasting plasma glucose concentration by 59 mg/dL from baseline in comparison to an increase of nearly 6.3mg/dL in patients undertaking a placebo [3].

Metformin is a "biguanide antihyperglycemic agent" as well as "first-line pharmacotherapy" utilized for the effective management of diabetes type 2. Mechanisms of action in the case of metformin are completely unique. Metformin reduces glucose levels in the blood by diminishing glucose production in hepatic cells, reduces glucose absorption in intestinal cells, and enhances insulin sensitivity by increasing glucose uptake and its utilization. Studies have further highlighted that the activity of mitochondrial complex I is inhibited by metformin and it has been postulated that potential antidiabetic effect occurs through a specific mechanism. After ingestion of metformin, "organic cation transporter-1" transports the drug into hepatocytes. Since the drug is positively charged, it accumulates within mitochondria due to the presence of membrane potential across the inner membrane of mitochondria and plasma membrane. Mitochondrial complex-1 activity isinhibited by metformin, preventing mitochondrial ATP production and resulting in enhanced cytoplasmic AMP: ATP as well as ADP: ATP ratios. These changes result in the activation of "AMP-activated protein kinase" which plays a significant role in glucose metabolism. Furthermore, enhancement of the AMP: ATP ratio inhibits "fructose-1, 6-bisphosphatase enzyme" resulting in further inhibition of gluconeogenesis [2]. In the intestine, metformin enhances the concentration of metabolism of anaerobic glucose in enterocytes, resulting in a reduction of "net glucose uptake" and enhanced lactate delivery to the liver. Studies have further implicated the gut as the primary action site for metformin.

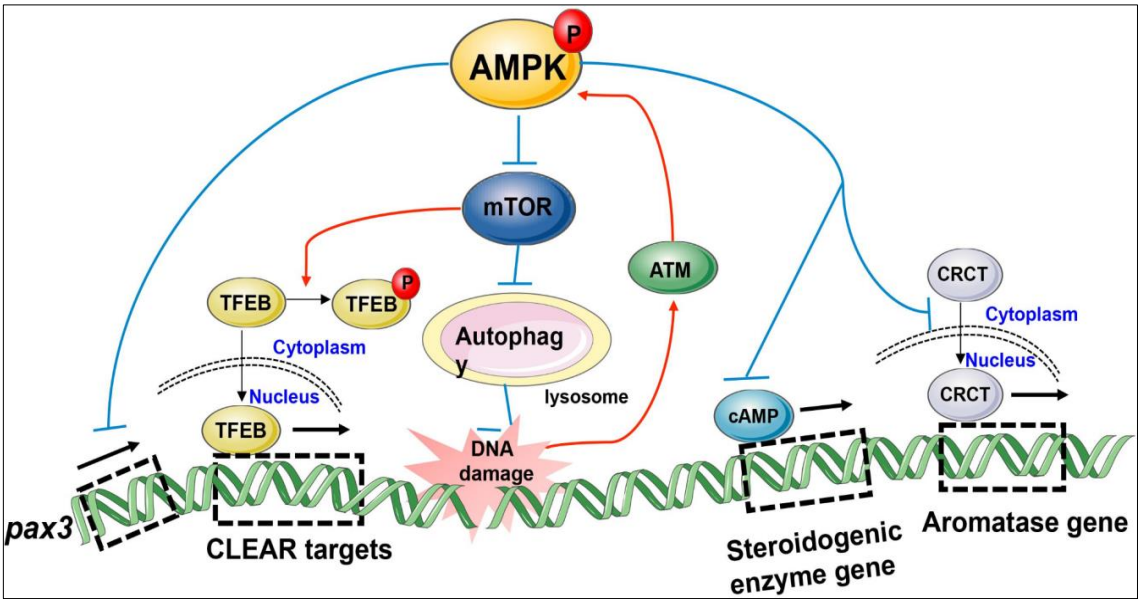

Fig 1: Working process of AMP-activated protein kinase

Impairment of lung function accompanying DM is mild but it can even become clinically important when individuals suffer from chronic cardiorespiratory conditions. DM Is a common form of comorbidity in COPD. Irrespective of the evidence associating DM with respiratory impairment, there are no studies that accurately examine the respiratory impact of insulin. Metformin is used for regulating hyperglycaemia and directly enhances the insulin sensitivity of the end organ. Several study findings have further highlighted that the usage of metformin in patients with COPD and T2DM enhanced the risk of bacterial pneumonia. T2DM is directly related to the prognosis and progression of COPD. High COPD exacerbation leads to high limitations of airflow, hospitalization, and respiratory failure. Individuals with "acute exacerbated COPD" have low vitamin B12 [5]. Usage of metformin for the long term in case of reduced serum vitamin B12 affects the normal functioning of respiratory muscles. Metformin is involved with enhanced respiratory outcomes. In order to determine the linkage between metformin usage and respiratory outcome in COPD patients, an observational study has been conducted. Study results highlighted that tidy results highlighted that 3969 individuals suffering from COPD having baseline medication and follow-up were identified.

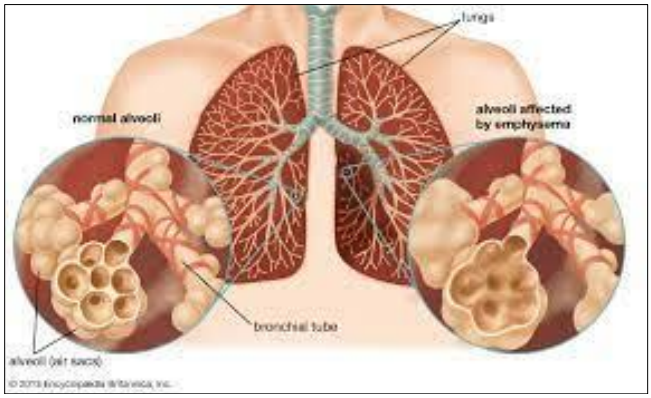

Fig 2: COPD

Participants using metformin were older and had an increased number of comorbidities. Severe exacerbations with a "total exacerbation rate of 0.64" and a "severe exacerbation rate of 0.24" were recorded. Numerous impacts have been observed beyond improvement in glucose tolerance and insulin sensitivity involving amelioration of airway inflammation. The report further suggests metformin inhibits the proliferation of airway smooth muscles through AMPK-associated inhibition of "TGF-β1 signalling", which

further leads to impairment of ASM bronchorelaxation. Metformin further reduces inflammation of the eosinophilic airway in the case of the allergic asthma model. Study findings further highlighted that metformin initiation was related to SGRQ improvement among patients with ACO. The report further suggests that medication plays a crucial role in reducing the regular impact of asthma on "quality of life" and disease exacerbation.

Oxygen therapy improves the patient's survival rate with hypoxemia and lung disease. Mechanical ventilation is crucial life-support in case of respiratory distress. Slowing along with sustained airflow to distal airspace reduces airflow turbulence, airway resistance, and efforts required for breathing and relieve hypercapnic respiratory failure. An observational study in 17 patients reading metformin usage for 6 months resulted in diminished dyspnoea symptoms and contributed towards improved health conditions [4]. Mitochondria are responsible for oxygen consumption. Metformin is capable of inhibiting complex 1, thereby diminishing ATP production and leading to mitochondrial dysfunction and energy stress. Metformin further diminishes mitochondrial respiration within skeletal muscles. Insufficient energy within respiratory muscles affects pulmonary function and mitochondrial dysfunction in skeletal muscles. Furthermore, metformin usage enhances the chances of the occurrence of bacterial pneumonia and increased cases of hospitalization due to COPD. Leading towards hypercapnia respiratory failure and requiring the support of mechanical ventilation.

Materials and Methods

Study design

Patients with symptomatic COPD, decreased glycemic control, and diabetes type 2 who were neither Obese nor overweight and between the ages of 18 and 75 were the subjects of a prospective observational open-label trial. Outpatient clinics or advertisements were used to find participants. All who participated in the initial screening provided their informed permission. Spirometry was evaluated to use an electronic spirometer throughout accordance to ATS/ERS guidelines 14 moments after breathing Salbutamol 400 mcg using a divider. Blood was taken in order to evaluate the kidney, hepatic & clotting processes. Then, the eligible individuals went to a baseline appointment for a number of procedures. A test that involved an incremental shuttle walk was used to gauge one's ability to exercise. The St. George's Respiratory Questionnaire was utilized for evaluating health-related quality of life (SGRQ). Dyspnea was quantified with the Baseline Dyspnea Index (BDI). The CHAMPS survey was used to gauge habitual physical activity. We measured both static and dynamic lung capacity and gases exchange (DLCO), nitric oxide exhaled, and respiratory mouth pressures.

Everyone who participated started taking metformin following this visit at a 500 mg twice day at first, increasing to 825 mg on two separate occasions following 4 weeks. Every six weeks, there were three intermediate follow-up visits for the subjects. During these visits, a transitional dyspnea index (TDI) questionnaire was given, as well as new measurements of waist and hip circumference, body weight, venesection, spirometry, and handgrip strength.

Inclusion and exclusion criteria

Participants were adults (18-75) with a poor glucose tolerance (IGT), severe COPD (GOLD stage 2 or more on post-bronchodilator respiratory function), BMI > 25, kg/m^2, and nutrition type 2 diabetic mellitus (T2DM).

The participants were not eligible for the study if they have chronic heart failure or congestive heart failure liver respiratory failure and fail or any other respiratory diseases present, cirrhosis of the liver, who are alcoholic (weekly 21units for males and 14 units for females), history of lactic acidosis, GFR < 45 ml/min, or if the patients were on metformin, any other oral corticosteroids, or hypoglycemic agents.

Statistical analysis

Data entry and statistical analysis were done using ANOVA statistical software. The proper percentage comparisons between the various groups were made using a Chi-square, the student's t-test, these same average scores, as well as the standard deviation and variance. Significant data was defined as a P value of 0.05.

Ethical approval

The authors gave the patients a full explanation of the study. The patient's consent has been obtained. The study's methodology has indeed been approved either by the hospital's ethical review board.

Results

The individual baseline characteristics are shown in Table 1. The research examined 80 individuals in total. 68% of the participants are males in the age group of 45-78, 17cm in height, and 86.2 kg weight with a mean BMI of 25.4. The participants smoke a minimum of 33 packets of cigars per year. 49% of participants are diagnosed with asthma, 16% with impaired 17% had diabetes of type 2, 86% had impaired fasting glucose levels, and there was no difference in glycemic control. The dyspnea index at baseline is 6. 63% of participants are with COPD GOLD stage II. The ratio of FEV1/FVC at baseline is 0.52. “

Table 1: Baseline participant characteristics

	Median (range)
n	80
Male (%)	68
Age (years)	63 (45-78)
Height (cm)	178 (156-189)
Weight (kg)	86.2 (65.2-151.2)
BMI (kg/m2)	25.4 (23.5-53.2)
Pack decades (smokers only)	33 (12-116)
Asthma diagnosis (%)	49
eGFR (mL/min)	81 (56 -119)
Low fasting glycemia (%)	86
Reduced tolerance to glucose (%)	16
Diabetes mellitus type 2 (%)	17
mmol/mol HbA1c	45 (39-63)
(% anticipated) FEV1	61 (31 -76)
FVC (% anticipated)	83 (53 -112)
Ratio of FEV1/FVC	0.52 (0.24-0.75)
Ratio of FEV1/FVC (% expected)	65 (32-95)
Stage II GOLD	63
Stage III GOLD	32
DLCO (L)	22.0 (11.5-36.2)
DLCO (% predicted)	82 (51-139)
Baseline dyspnea index (BDI)	6 (1-13)

The alterations in general health and symptoms are listed in Table 2. The SGRQ's overall score increased by a mean of 5 points, which is more than double the minimum change that is clinically relevant (4 points). A tendency towards a small improvement could be observed in the test of the mean stepwise shuttles walk (ISWT).

Table 2: Changes in symptoms and status of health

Variable	Initial Median (range)	26th week median (range)	Alter the median (range)	p value
SGRQ rating (total)	46 (12-71)	38 (2-67)	-4 (-28-7)	0.0050
SGRQ rating (symptoms)	64 (5-100)	51 (7-83)	-10 (-58-23)	0.0938
SGRQ rating (activity)	55 (19-85)	47 (0-84)	-2 (-55-16)	NS
SGRQ rating (impacts)	31 (0-78)	29 (0-59)	-5 (-31-5)	0.0041
Index of transitional dyspnea (total)	-	3 (-4-6)	-	0.0113
Index of transitional dyspnea (functional limitation)	-	0 (0-2)	-	0.0360
Index of transitional dyspnea (magnitude of task)	-	1 (-2-2)	-	0.0283
Index of transitional dyspnea (the size of effort)	-	1 (-1-2)	-	0.012
Short walk to the shuttle (m)	251 (91-529)	340 (120-640)	15 (-60-140)	0.1136
Borg's final test result	5 (1-6)	4 (1-6)	-1 (-5-3)	0.0440

Table 3 displays the modifications to gas exchange and nitric oxide exhaled as well as lung function. During the course of the trial, inspiratory mouth pressures (PImax) increased. With the exception of two subjects, PImax rose by, on average, 7.5 cm H_2O. Expiratory mouth pressures did not significantly vary, and grip strength somewhat declined.

Table 3: Displays the modifications to gas exchange and nitric oxide exhaled as well as lung function

Variable	Initial Median (range)	26th week median (range)	alter the median (range)	p value
FEV1 (L)	1.56 (0.89-3.05)	1.68 (0.86-3.43)	0.02 (-0.32-0.63)	NS
(% anticipated) FEV1	66 (35-79)	61 (27-83)	2 (-6-17)	NS
FVC (L)	3.40 (2.05-5.56)	3.46 (2.15-5.33)	0.05 (-0.63-0.87)	NS
FVC (% anticipated)	85 (52-112)	90 (59-103)	3 (-15-23)	NS
Ratio of FEV1/FVC	0.56 (0.24-0.71)	0.53 (0.26-0.65)	0.02 (-0.13-0.12)	NS
FEV1/FVC ratio (% predicted)	66 (32-90)	71 (33-86)	3 (-16-14)	NS
TLC (L)	6.55 (4.34-9.92)	6.31 (4.19-9.87)	-0.16 (-0.57-0.42)	0.0992
TLC (% anticipated)	103 (83-138)	104 (83-135)	-4 (-6-7)	0.1472
RV (L)	3.26 (1.75-4.45)	2.84 (1.47-4.32)	-0.26 (-0.94-0.50)	0.1204
RV (% anticipated)	135 (86-173)	121 (62-173)	-12 (-33-26)	0.0831
RV/TLC ratio	0.42 (0.33-0.64)	0.42 (0.25-0.53)	-0.02 (-0.11-0.06)	0.1164
Ratio of RV to TLC (% anticipated)	113 (86-157)	116 (63-145)	-4 (-32-16)	0.1295
FRC (L)	3.83 (2.34-5.62)	3.37 (2.24-5.86)	-0.07 (-0.76-0.32)	NS
FRC (% predicted)	113 (81-163)	106 (84-172)	-1 (-16-7)	NS
VC (L)	3.54 (2.15-5.64)	3.53 (2.13-5.53)	0.03 (-0.44-0.67)	NS
DLCO (L)	21.3 (10.5-38.3)	19.4 (10.3-32.3)	-0.4 (-5.3-2.5)	0.0881
DLC (% anticipated)	86 (54-139)	82 (46-143)	-3 (-22-11)	0.0733
ENO (ppb)	37 (6-222)	26 (12-133)	-3 (-84-51)	NS

The majority of individuals had moderately severe baseline AFO, but gas trapping was common (Table 4). Spirometry & gas transport was relatively constant throughout the study. The RV/TLC ratio, TLC, and TLC/RV all displayed negative trends. CRP, LDL, and total cholesterol levels were all heading downward. ENO or other lipid indicators did not alter considerably.

Table 4: Changes in the strength of respiratory and general muscle strength

Variable	Initial Median (range)	26th week median (range)	Alter the median (range)	p value
PImax (cmH_2O)	66 (25-156)	75 (51-163)	6.9 (-7.5-50.3)	0.007
PImax (% predicted)	75 (37-134)	80 (53-141)	6 (-13-63)	0.016
PEmax (cmH_2O)	93 (55-172)	106 (56-233)	2 (-30-46)	NS
PEmax (% predicted)	55 (32-88)	57 (33-103)	2 (-19-33)	NS
Average grip force, dominant hand (kg)	30 (20-59)	32 (19-60)	-1.2 (-9.8-2.5)	0.0445
Average grip force, dominant hand (% expected)	82 (64-122)	75 (56-123)	-2.9 (-30.7-5.2)	0.0393
Strongest grasp possible, dominant hand (kg)	32 (20-62)	35 (17-60)	-1.5 (-10.1-3.3)	0.0241”

Discussion

The mechanism associated with the relation between DM and impairment of lung function is unknown similar to the unknown effect of antidiabetic agents on the respiratory system. Several studies have focussed on assessing whether treatment with metformin enhances lung function or COPD symptoms among individuals and glucose intolerance. Study participants included individuals belonging to the age group

18 to 75 who were obese with COPD symptoms. However, individuals who had a history of chronic respiratory failure, hepatic cirrhosis, respiratory disease, and liver failure were not included in the study. Initial screening was done on participants and spirometry was measured by following ATS/ERS guidelines after 15 minutes of inhalation of 400mcg salbutamol through a spacer. Blood was drawn for measuring renal and liver function. Eligible participants then went for baseline visits. A shuttle work test was performed for assessing exercise capacity. SGRQ was used for measuring health-related life quality. "Baseline Dyspnoea Index (BDI)" was used for the assessment of dyspnoea and the CHAMPS questionnaire was used for assessing physical activity [6]. Furthermore, respiratory mouth pressures along with "exhaled nitric oxide", and "Dynamic and static lung volumes" were measured by following ATS/ERS guidelines. Metformin was administered to all participants, initially providing 500mg twice and then increasing it to 850mg twice after a month. Follow-up visits were scheduled after every 6 weeks. Study results highlighted that a total of 17 participants completely went through the examination procedures. Nearly 76% of the study participants were from European ethnicity while 59% were current smokers. Metformin associated with severe adverse impact did not occur. According to the Health status the SGRQ score improved by 5 points. Improvement in the "shuttle walk test" was also observed. Baseline severity in the case of AFO was moderate for the majority of the participants while trapping of gas was common. Significant changes in gas transfer were not observed during the study. Trends were observed in reduced RV/TLC ratio, TLC, and RV. "Inspiratory mouth pressures" enhancement occurred during the study however, significant changes were not observed in the case of "expiratory mouth pressure". Trends in CRP reduction, and LDL cholesterol were observed while significant changes were not observed in the case of lipid markers.

Metformin has been considered to be one of the ideal agents for gaining a detailed understanding of antidiabetic therapy in case of respiratory disease. It is an oral medication that acts through numerous mechanisms for controlling hyperglycaemia and enhances "end-organ insulin sensitivity". Metformin acts through AMPK, an enzyme that is present in almost all cells and mimics the impact of caloric restriction, inhibits rapamycin, and activates antioxidant defence. SGRQ was used among patients suffering from chronic airway disease. The total score in SGRQ showcased improved clinical and statically significant outcomes over the follow-up period. "Transition dyspnoea index (TDI)" showcased clinically significant outcomes [8]. Changes in TDI and SGRQ highlighted metformin produced symptomatic benefits in the case of COPD. The result in context to pathophysiological aspects highlighted a reduction in tissue glycosylation, airway inflammation, and enhanced skeletal muscle function.

"Pulmonary arterial hypertension (PAH)" is a rare form of the disease associated with enhancement of "pulmonary arterial pressure" and "pulmonary vascular resistance" leading to hypertrophy of the right ventricle. Advancement in disease treatment and development has been achieved in the last 15 years however, PAH pathogenesis remains un-cleared. Metformin has been used for more than 40 years in case of treatment of hyperglycaemia but currently, it has been described as a pleiotropic molecule. Metformin diminishes several other cardiovascular risk factors and it also enhances endothelial function. Furthermore, metformin restores microvascular reactivity to bradykinin, acetylcholine, and histamine. In the case of diabetic patients, the lung is the target organ for "diabetic microangiopathy". Several other defects involved with DM also lead to diminished lung function like "pro-inflammatory state", "respiratory autonomic neuropathy" and "ultrastructural anatomic defects". A high rate of T2DM in COPD patients has been demonstrated, however, the mechanism associated with the onset of "respiratory dysfunction" in the case of diabetic patients remains speculative. "Oral hypoglycaemic agents" affect lung function. Metformin has several pleiotropic properties that reduce inflammation as well as oxidative stress. In the case of animal experiments, metformin has resulted in decreasing parenchymal fibrosis, eosinophilic inflammation, and airway remodelling. In individuals with T2DM and COPD, treatment associated with metformin reduced hospitalization visits. "Glucagon-like Peptide-1 Receptors (GLP-1R) agonists" having "insulin secretagogue effect" modulate pulmonary function [7]. Studies further highlighted GLP-1 enhanced secretion of airways macromolecules and relaxation of smooth muscles of arteries have been also observed. Study results indicated that treatment with "GLP-1R agonists" enhanced airway function irrespective of glucose level in blood in T2DM patients without any pulmonary disorder. Correlation between change in case of lung function and "change in HbA1c" has not been observed.

The control cohort however showcased an increase in FEV1; however, the results were not statistically significant. In the case of treatment of patients with GLP-1R agonists, effective results were obtained for secondary outcomes. In the case of the control cohort, treatment of patients with metformin alone accelerated not only the numerical value for FEV1 but also improved FVC. Such an effect has been directly related to the pleiotropic action of metformin on lung tissues. Drug administration reduces airway remodelling and inflammation, peribronchial as well as parenchymal fibrosis [5]. Modifications in lung function were not at all observed among T2DM subjects included within the insulin cohort, irrespective of the treatment of the patients with metformin. This could be due to antagonistic interaction occurring between "pleiotropic actions of metformin" resulting in ASM relaxation and enhanced "contractile ASM tone" induced through insulin usage. Hyperinsulinemia without or with insulin resistance is related to diminished lung function. Metformin along with GLP-1R agonists diminishes ASM contractility while acting upon different receptors [7]. GLP-1R diminishes airway inflammation as well as mucus secretion in the case of ovalbumin-induced asthma. Since the impacts of GLP-1R agonists are reduced by GLP-1R antagonists and rely on AMPK and PKA inhibitors, the PKA-AMPK pathway is directly associated with the beneficial impact of GLP-1R agonists in the case of human ASM. GLP-1R further controls intracellular pathways and is analogous to the ones activated by β2-AR agonists, thus indicating a "synergistic Broncho-relaxant effect" while combining GLP-1R agonists with "antimuscarinic agent". Thus the prospective studies in the context of metformin therapy in the case of COPD highlighted clinical as well as statistical improvement observed in inspiratory muscles, and health status. Correction in BMI showcased significant changes.

Metformin had a reduced effect on RER, HR, VO2 peak, and VE. Metformin has been reported to impair VO2 peak by obstructing the mitochondrial ET system. Metformin is prescribed for the management of hyperglycaemia among individuals suffering from diabetes as well as to delay the transition to diabetes. Healthy individuals were also examined for avoiding complications of mitochondrial myopathy or hyperglycaemia.

Conclusion

In conclusion, metformin is an effective "antidiabetic therapy" for the management of type 2 diabetes. It can reduce glucose production in hepatic cells, diminishes glucose absorption in intestinal cells, and enhances insulin sensitivity by increasing glucose uptake and utilization. Its unique mechanism of action also involves the inhibition of mitochondrial complex-1 and activation of AMP-activated protein kinase. The study suggests that metformin may improve lung function and symptoms in individuals with COPD and glucose intolerance. In addition, metformin treatment in individuals with COPD showed improvements in lung function, inspiratory muscles, and health status, with a reduction in airway remodelling and inflammation. Furthermore, the above discussion has found that it has an adverse impact on the VO2 peak cause of disruption of the mitochondrial ET system. Whenever we discussed metformin with GLP-1R agonists with "antimuscarinic agent" it explored further advantages in decreasing airway inflammation and bronchoconstriction. Therefore, it has been required further research to investigate the long-term effects of these medicines. On the other hand, the medicine was effective with it had no harmful side effects. Therefore, these benefits reported in SGRQ and shuttle walk tests were ascribed to the many modes of action of metformin. For example, its impact on PKA-AMPK as well as antioxidant defense. Furthermore, the physiological respiratory development in people on metformin therapy demonstrated that there were no essential variations in pulmonary function among the metformin group. Moreover, it implies that metformin did not have a major effect on pulmonary performance in 2 types of diabetes patients.

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