

## Review Form 1.6

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Manuscript Number:	Ms_JPRI_81218
Title of the Manuscript:	Metformin, a systematic review
Type of the Article	Review Article

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**PART 1:** Review Comments

	Reviewer’s comment	Author’s comment (if agreed with reviewer, correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)
<b>Compulsory</b> REVISION comments	<p>Please kindly note that the text has problems related to the English language.</p> <p>I have corrected some mistakes, however, some linguistic expressions are still difficult to understand.</p> <p>It would be preferable if the manuscript was corrected by a native English speaker, if possible.</p> <p>Metformin, a systematic review</p> <p>ABSTRACT: Metformin has been found to be the main pharmacologic treatment of <del>type II</del> <b>Type II</b> Diabetes also the most recommended drug around the world, either alone or in blend with insulin or other <del>glucose lowering</del> <b>glucose-lowering</b> treatments. Metformin is a biguanide. Metformin was likewise removed because of worries over lactic acidosis, but it consequently brought down glucose levels and was once again introduced in 1995.</p> <p>Diabetes mellitus, <b>is</b> a gathering of issues related to <b>a</b> metabolism where the glucose concentration of blood is higher than <del>normal</del>, <b>normal</b>, because of low discharge of insulin either inappropriate reactivity to insulin , <b>insulin</b>, bringing about hypertension. There fore <b>Therefore</b> low glucose, which <del>results</del> <b>results to</b> cut off intricacies. Metformin has indicated <b>been indicated</b> to forestall diabetes for individuals who pose greater danger also reduction in the majority of diabetic confusions. Late responses of metformin, indicated many more ramifications, for example, metformin has kidney protective characteristics.</p> <p>With an expanding worldwide weight of CAD (<b>I think it is preferable to write the acronym the first time</b>), early identification and convenient administration of hazard factors are pivotal to <del>decrease</del> <b>decreasing</b> dismalness and mortality in such patients. DM is viewed as a free danger factor for the improvement of CAD. Metformin, a drug for diabetic medication, has <del>role</del> <b>a role</b> in pre-clinical and clinical examinations, to lower cardiovascular occasions in <del>the</del> DM patients. Metformin protectively affects <del>coronary vein</del> <b>coronary vessels</b> past its hypoglycemic impacts. Given its worldwide accessibility, course of organization and cost, metformin gives an extra restorative choice for essential and optional anticipation of CAD in DM and non-diabetics.</p> <p>Metformin has also <del>showed</del> <b>shown</b> remarkable improvements in patients with Polycystic ovarian syndrome.</p> <p><b>Keywords</b> – Metformin, lactic acidosis, type II diabetes mellitus, kidney protective, poly-cystic ovarian syndrome.</p> <p><b>INTRODUCTION</b> A cluster of metabolic issues <del>are</del> <b>is</b> related to diabetes wherein the glucose of <del>blood showed</del> <b>blood showed</b> increase than the ordinary <del>bars</del> <b>(?)</b> because there is low insulin <del>discharge</del> <b>either-discharge either</b> inappropriate reactivity to insulin, bringing about hypertension. The low <b>(?)</b> glucose condition delivers the traditional</p>	

	<p>manifestations of polyuria, polydipsia <del>also increase</del> <b>also increase</b> in appetite. It might disrupt functions related to <del>neural</del> <b>the neural</b> system, issues to renal, visual deficiency, <del>appendageal</del> <b>(?)</b> loss, problems related to intercourse, rise in coronary failure either stroke [1]. <del>Metformin</del>, <b>Metformin</b>, which is a biguanide, regulates glucose levels of blood ,hence decrease these problems. Metformin acts by assisting <del>reaction of body</del> <b>the reaction of the body</b> to insulin. Also diminishes the measure of <del>glucose produced</del> <b>glucose produced by liver the liver</b> and <del>of by</del> the digestion tracts or absorption in <del>stomach the stomach</del>. [2] Other than its action to lower glucose, <del>metformin are advised</del> <b>metformin is advised along with</b> dietary changes and exercises to forestall diabetes in individuals having <del>high</del> <b>a high</b> risk for getting diabetes. In females, <del>#</del> it is likewise <del>utilized</del> <b>utilised having</b> poly-cystic ovarian syndrome. Metformin might make better <del>standardisation</del> <b>standardization</b> of menstrual cycles and improved fertility. [3] Metformin was blended and observed to diminish glucose levels in <del>blood in</del> <b>blood in 1920s the 1920s</b>; be that as it may, it wasn't utilized for a time. Utilization of metformin was revived in year 1957, at the point when the results of a clinical primer were <del>dispersed</del> <b>(?)</b> certifying its effect on diabetes. Metformin is presently broadly endorsed as a medication for high blood glucose; carrying a plethora of side effects, particularly ketoacidosis. [4] Recently, not just a few ramifications have been found for metformin, yet in addition reports demonstrate that the drug has unfavorable impacts which are immaterial when its advantages are seen altogether. [3] Theoretically, the utilization of the drug <del>have</del> <b>has</b> been disallowed in a huge gathering of patients <del>having Diabetes</del> <b>having Diabetes Mellitus type II</b> due to lactic acidosis danger. Nonetheless, it has been displayed that <del>couple</del> <b>a couple</b> of patients having <del>diabetes of whom</del> <b>diabetes of who</b> are viewed as in danger have gotten Metformin with no expanded lactic acidosis danger. [2,3,4,5] Besides, as of late a few papers have been distributed demonstrating renoprotective properties for metformin.</p> <p><b>MECHANISM OF ACTION</b></p> <p>Studies have shown that metformin acts in the liver, where it restrains gluconeogenesis by hindering <del>a</del> mitochondrial redox transport. Medication's belonging <del>are</del> is probable pleiotropic. Metformin has likewise been demonstrated to be an insulin sensitizer and to probably act in the gut lumen through different components. [6]. Applications of Metformin in various conditions</p> <p><b>DIABETES MELLITUS</b></p> <p>Metformin drug is fundamentally utilized for type II diabetes mellitus treatment, especially in patients of obese nature. Metformin drug has been displayed to have <del>decreased death</del> <b>decreased death</b> and <del>disarrays in</del> <b>disarrays in</b> diabetes by about a third contrasted with <del>chlorpropamide</del>, with chlorpropamide, glibenclamide, <del>and</del> <b>and</b> insulin. [5] Metformin diminishes glucose level in serum by a few unique components <b>(?)</b>, prominently through non-pancreatic systems without increasing discharge of insulin. The impacts of insulin are built; henceforth, is named "sensitizer of insulin". Metformin likewise stifles the liver for its glucose creation, which is chiefly because of <del>decreased</del> <b>the decreased</b> pace of gluconeogenesis also a little impact on glycogenolysis. Besides, metformin enacts the compound adenosine monophosphate kinase bringing about restraint of main proteins engaged with gluconeogenesis and of glycogen combination in the hepatocytes while animating insulin flagging and transport of glucose in muscle cells. AMPK manages both cellular with organ digestion and decline in any energy in hepatocytes, <del>prompts</del> <b>prompting</b> AMPK enactment. This review to a degree has progressed to explain the part of metformin movement on gluconeogenesis in hepatocytes. [7,8]</p> <p>Besides, metformin fabricates the periphery glucose expulsion that arises commonly through extended non-oxidative glucose removal into voluntary muscles. Generally, it doesn't lower glucose levels and this reason be taken as a remarkable enemy <b>(?)</b> of drugs of diabetes. [9]</p> <p>Diabetic treatment with metformin is related with decrease <del>ingain</del> <b>in gain</b> of weight contrasted and insulin and sulfonylureas. Glucose is controlled better in weight gain instances. A review has shown that, on a <b>ten-years</b> period of treatment, <b>metformin-</b></p>	
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	<p><del>treated</del> patients acquired around 1 <del>kilograms</del>-kilogram, <del>glibenclamide-treated</del> patients acquired around 3 kilograms, <del>insulin-treated</del> patients acquired <del>six</del> 6 kg weight.[10]</p> <p><b>Poly-Cystic Ovarian syndrome</b> <del>Poly-cystic</del> The <del>poly-cystic</del> ovarian syndrome is often connected with insulin resistance and starting around 1994 in PCOS treatment, metformin was put forward.[11] In the year 2004, National Institute for Health and Clinical Excellence prescribed metformin for females having Poly-cystic ovarian syndrome and an index of body mass over 25 for both infertile and <u>anovulated</u> (?) cases when different treatments fail to deliver satisfactory results.[12] However, a few ensuing audits didn't show promising outcomes and didn't suggest it further or possibly as a first-line medication,[13] aside from females with glucose intolerance.[14] The rules for the most part propose clomiphene to be the principal treatment and suggest a way of life change autonomous from drug treatment.</p> <p>An orderly survey utilizing relative preliminaries like metformin, clomiphene discovered equivalent outcomes for infertile cases[15]. A BMJ publication said metformin ought to be utilized as a subsequent option, whether a failure is seen in the treatment of clomiphene.[16] Besides, an enormous audit utilizing twenty-seven clinical preliminaries observed that metformin wasn't related to any increment in live birth quantity; notwithstanding, ovulation rates were enhanced, particularly if clomiphene was mixed with it and utilized.[17]</p> <p>An audit suggested metformin is the best option due to constructive outcomes over insulin obstruction(?), hirsutism, anovulatory cases, and weight, many are regularly connected with poly-cystic ovarian syndrome.[18]</p> <p>Diverse preliminary plans may be the explanations behind the problematic outcomes. For instance, considering rate of live birth rather than pregnancy as the endpoint would have one-sided a couple of preliminaries opposing metformin.[19] Different clarification says that metformin might have diverse adequacy in various populaces</p> <p><b>As an Adjuvant Treatment for Cancer</b> Examination proposes that metformin can work as a valuable adjuvant specialist, especially in prostate and also colorectal malignant growth. A quantity number of studies recognized that every growth type is probably going to mirror the occurrence and socioeconomics of the illness, especially the probability of showing with beginning phase sickness and an analysis of diabetes mellitus. An idea of randomized clinical preliminaries utilizing metformin as an adjuvant, along with the most grounded aiding proof in prostate along with colorectal malignant growth, especially who got treatment with revolutionary radiation therapy. [20]</p> <p>The variety in the adjuvant impacts of metformin as indicated by the type of cancer can be clarified by contrasts in patient qualities and growth science (Linguistic expression difficult to understand). Metformin impact on AMPK flagging have has been conjectured as a significant route by which metformin applies upon the targets of malignancy impacts [21]. AMPK flagging dysregulation is additionally connected with the metabolic disorder [22], a group of situations which that incorporate raised blood glucose before meal, hyperlipidaemia hyperlipidemia, hypertension with obese condition [23]. Disorders related to metabolism is additionally seen building danger of fostering a few malignancies, especially colorectal disease [24], where it is likewise connected with less fortunate repeat and endurance results [25]. Moreover, it is referred to create as an outcome of androgen hardship treatment in men with prostate malignant growth [26]. Metformin might further develop OS by decreasing the number of deaths due to heart ailments related with metabolic disorder to the metabolic disorders; in any case, the enhancements in RFS and CSS recognized recommend an immediate target of malignant growth impact. In prostate malignancy, our review bunch examination recommends that the gainful impacts of metformin use could be restricted to those going through extensive radiation therapy. Pathway of AMPK is understood to assume</p>	
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	<p>a part in controlling cell reactions in radiation therapy, [27] considers to xenograft models of rat recommend metformin, which can further develop growth oxygenation along with thusly radiations [28].</p> <p>Restrictions of meta-examination incorporate innate shortcomings of information that are observed, especially greater estimation blunders within the openness to metformin, variety in the use of metformin, also the danger of predispositions related to time [29]. Serious levels in variety among the aftereffects of researches—was were noticed for some results researched in a large portion under types of malignancy. <b>Affectability (Linguistic expression difficult to understand)</b> investigations done were to intend and investigate potential explanations behind these to illuminate further observational along with clinical preliminary plan; notwithstanding, just a few examinations were conceivable because of inadequate review digits. Both colorectal and prostate malignancy, overall impact amount seemed as a increment for examines along with <b>follow-up</b> of three years, even more noteworthy, featuring about the significance of guaranteeing satisfactory span in following up for later investigations. Likenesses <del>has</del> <b>have</b> been found among investigations of headache medicine, in which more prominent advantages <del>has</del> <b>have</b> been seen having longer <del>followup</del> <b>follow-up</b> [30-32]. A predetermined amount of researches explored the connection about the recurrence, portion and span of metformin in beginning phase malignancy; be that as it may, discoveries are conflicting and further examination is needed to all the more likely comprehend this relationship.</p> <p>Past examinations have recommended that an analysis of diabetes mellitus adversely affects disease results [33,34]; in this manner, consideration of non-diabetes mellitus victims in comparator gatherings would be little about the valuable impact that metformin produced. Attributable to lacking review sets, that was simply conceivable to examine the impact about the presence or nonappearance about the non- diabetes mellitus patients in the comparator bunch for RFS seen in prostate disease, in which there was no proof about the impact.</p> <p>Examination about metformin in the essential anticipation setting shows various difficulties, where the harmony between <del>unfavourable</del> <b>unfavorable</b> impacts and advantages is probably going to be low good, also hard to recognize in preliminary clinicals on account of less occasion rate. Whereas the <b>high-level</b> system can give an adequate occasion rate, where there is proof proposing that metformin needs lengthy haul use to apply target enemy of malignancy impact [35], and in this way, patients with set up disease with more restricted forecasts will most likely be unable to get metformin for long which would be enough to arise helpful advantage <b>(Linguistic expression difficult to understand)</b>. Accordingly, the adjuvant quality could generally be reasonable about researching of counter malignant growth impacts of metformin.</p> <p><b>Lactic Acidosis</b></p> <p>Instances of lactic acidosis keep on being reported in patients who are prescribed metformin. In a study, out of a million patients who were prescribed metformin in the U.S., there were forty-seven reports (twenty lethal) of lactic acidosis. Out of the observed patients, forty-three were found to have renal problems (important metformin contraindication) or other risk factors for lactic acidosis other than metformin (essentially cardiovascular breakdown due to congestive causes) [36]. <b>The</b> death rate in patients having <b>metformin-related</b> lactic acidosis has all the earmarks of being ~40% and furthermore gives off an impression of being related <del>with</del> <b>to</b> cardiovascular breakdown [36,37]. <b>It</b> was observed that out of all patients, only four didn't show other risk factors of lactic acidosis after metformin <b>was</b> administered. This study also indicated that out of the four case subjects, lactic acidosis had been accelerated by a scene of urosepsis. In one of these four case subjects, lactic acidosis seems to have been accelerated by a scene of urosepsis. The patients did not pass on.</p> <p><b>A</b> new audit of Stadesetal. [37] gives extra proof about major instances of metformin drug-related lactic-acidosis, especially lethal types, which are identified with hidden conditions as opposed to metformin. The creators proceeded to ascribe several reports about metformin related lactic-acidosis to a distribution predisposition where the</p>	
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	<p>broadly held tested impression that lactic acidosis caused by metformin is wrongly strengthened.</p> <p>Lactic acidosis happens among non-diabetic victims in relationship with disease, malignant growth, disorders of liver, <del>with</del>-kidney disappointment, and also quite often a death harbinger except if the situation that is hidden is adjusted [38,39]. <del>Victims</del> suffering from <del>type II</del> diabetes, pace of lactic-acidosis accounted for [40], <del>should</del> be comparative among <del>patients using</del> metformin also in <del>victims who</del> never used metformin.</p> <p>Stacpoole [41] has proposed that <del>cases about metformin-related</del> lactic acidosis address "responsibility by relationship" <del>along with</del> phenformin. Stades et al. [37] ascribed several <del>cases about</del> metformin-related lactic acidosis to the incident that victims suffering from diabetes are inclined for fostering genuine ailments that lead to lactic acidosis. Besides, the absence of connection between's levels of lactate and levels of metformin in victims [42] unequivocally proposes <del>about</del> metformin, which is frequently a blameless spectator. The quantity of reported instances <del>about of</del> metformin-related lactic acidosis is little if someone thinks about ways metformin is utilized [37]. This metformin <del>have</del> <del>has</del> been utilized securely in victims with serious <del>post-drug</del> effects (43–48) can be observed as proof about <del>its not</del> causing lactic acidosis. Then again, instances from the metformin gluts about lactic acidosis (32), especially among youngsters with no hazard elements [33,34], recommend metformin causing lactic acidosis whenever administered in huge portions. Metformin infrequently, whether at any point, produces lactic acidosis at the time it is utilized according to the name. Metformin is related <del>with to</del> lactic acidosis in victims with situations that would themselves be able to produce lactic acidosis (cardiovascular breakdown, low oxygen, Sepsis, and so on) In any case, it is difficult to decide how much, assuming any, metformin might add among the advancement of lactic acidosis. At the point where metformin getting utilized according to the name, expanded danger of lactic acidosis is zero else thereabouts near zero so that it can't be considered in customary clinical dynamic. Metformin would be able to produce lactic acidosis, is upheld by the searching of lactic acidosis in individuals whosoever has taken gluts (?). Accordingly, amassing of the metformin in preparing kidney inadequacy may be relied upon to encourage lactic acidosis in certain victims in danger. In the event that one rejects excess dosage of glutes (?), most instances<del>about of</del> metformin related lactic acidosis, especially deadly types, <del>which</del>—were likely unbrought about by the drug metformin.[49-58]</p> <p><b>CONCLUSION</b></p> <p>Metformin has been in need for over 60 years is as yet the best option drug for T2D. After the underlying idea that metformin could give CV insurance, the extra information gathered shows <del>s</del> not just that the medication can be utilized all the more generously as for renal capacity, yet that it could add to renal assurance. <del>The</del> information additionally demonstrates <del>s</del> that metformin might decrease the danger of neurodegenerative conditions, and preliminaries are continuous to straightforwardly survey the antineoplastic properties of the medication. In any case, in spite of wide and long-standing involvement with the clinical utilization of the medication, its method of activity is as yet not completely comprehended, and the defensive activity it might apply on the CV framework, kidney, and mind and against disease is plainly generally free of its glucose-bringing down viability. The sub-atomic systems of activity for the most part include AMPK/mTOR pathway actuation, much in accordance with what occurs under states of energy limitation. These impacts might be considered as being somewhat like those created by SGLT2is, one more class of glucose-bringing down specialists with demonstrated cardiorenal security. The metabolic impacts of metformin and SGLT2is may to be sure have a few similitudes. For example, utilization of SGLT2is inspires a moderate expansion in plasma grouping of ketone bodies, an elective energy substrate that has been professed to add to their CV advantage. Curiously, metformin use is additionally connected with expanded blood levels of another elective fuel substrate, lactic corrosive. On top of this, proof exists for a basic job of the cell-to-cell lactate</p>	
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	<p>transport, with lactate being a functioning ligand to explicit receptors through which energy is monitored, mitigating reaction, insusceptible resistance, antifibrotic activity, quality versatility, etc, can be applied. For the treatment of type 2 diabetes mellitus, a drug of the biguanide class, Metformin can be used. It can be used in patients who are obese and stout and in patients with ordinary kidney loads.</p> <p>In patients with Diabetes mellitus (type 2), Metformin shows many benefits like weight reduction, reduced hyperinsulinemia, exaggerated fibrinolysis, improved profiles, and enhanced endothelial capacity. has a few advantages in patients with type 2 diabetes mellitus, including diminished hyperinsulinemia, weight decrease, increased fibrinolysis, further developed lipid profiles and upgraded endothelial capacity.</p> <p>Even though the utilization <del>of utilization</del> of metformin in the condition of diabetes has raised questions on normal wellbeing, its benefits and the new outcomes show that its nephroprotective action towards nephrotoxic specialists and its new great security date <del>have</del> <b>has</b> driven scientists to acknowledge the utilization of this medication.</p>	
<b>Minor</b> REVISION comments	<p><b>In the current historical context, it might also be interesting to consider the benefits metformin provides in the case of Covid 19 infection</b></p>	
<b>Optional/General</b> comments	<p><b>REFERENCES</b> are abundant, relevant, and well-chosen.</p> <p><b>The arguments related to metformin are valid.</b></p>	

**PART 2:**

	<b>Reviewer's comment</b>	<b>Author's comment</b> <i>(if agreed with reviewer, correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)</i>
<b>Are there ethical issues in this manuscript?</b>	<i>(If yes, Kindly please write down the ethical issues here in details)</i>	

**Reviewer Details:**

Name:	<b>Lorenzo Bracco</b>
Department, University & Country	<b>Italy</b>