Review Article

Metformin, a systematic review

ABSTRACT:

Metformin has been found to be the main pharmacologic treatment of typeII Diabetes also the most recommended drug around the world, either alone or in blend with insulin or other glucose lowering 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.

Diabetes mellitus, a gathering of issues related to metabolism where the glucose concentration of blood is higher than normal , because of low discharge of insulin either inappropriate reactivity to insulin , bringing about hypertension. There fore low glucose, which resultsto cut off intricacies. Metformin has indicated 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.

With an expanding worldwide weight of CAD, early identification and convenient administration of hazard factors are pivotal to decrease 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 role in pre-clinical and clinical examinations, to lower cardiovascular occasions in the DM patients. Metformin protectively affects coronary vein 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.

Metformin has also showed remarkable improvements in patients with Poly-cystic ovarian syndrome.

Keywords – Metformin, lactic acidosis, type II diabetes mellitus, kidney protective, poly-cystic ovarian syndrome.

UNDER REVIEW

INTRODUCTION

A cluster of metabolic issues are related to diabetes wherein the glucose of bloodshowed increase than the ordinary bars because there is low insulin dischargeeither inappropriate reactivity to insulin, bringing about hypertension. The low glucose condition delivers the traditional manifestations of polyuria, polydipsia alsoincrease in appetite. It might disrupt functions related to neural system, issues to renal, visual deficiency, appendagal loss, problems related to intercourse, rise in coronary failure either stroke [1]. Metformin , which is a biguanide regulates glucose levels of blood ,hence decrease these problems. Metformin acts by assisting reaction of body to insulin. Also diminishes the measure of glucoseproduced by liver and of the digestion tracts or absorption in stomach.[2] Other than its action to lower glucose,metforminare advised alongwith dietary changes and exercises to forestall diabetes in individuals having high risk for getting diabetes. In females,it is likewise utilizedhaving polycystic ovarian syndrome. Metformin might make better standardisation of menstrual cycles and improved fertility.[3] Metformin was blended and observed to diminish glucose levels in bloodin 1920s; 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 dispersed 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 have been disallowed in a huge gathering of patients havingDiabetes Mellitus typeII due to lactic acidosis danger. Nonetheless, it has been displayed that couple of patients having diabetesof whom 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.

MECHANISM OF ACTION

Studies have shown that metformin acts in the liver, where it restrains gluconeogenesis by hindering a mitochondrial redox transport. Medication's belonging are 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

DIABETES MELLITUS

Metformin drug is fundamentally utilized for typeII diabetes mellitus treatment, especially in patients of obese nature. Metformin drug has been displayed to have decreaseddeath and disarraysin diabetes by about a third contrasted withchlorpropamide, glibenclamide and insulin.[5]

Metformin diminishes glucose level in serum by a few unique components, 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 decreased 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 cellularwith organ digestion and decline in any energy in hepatocytes, prompts AMPK enactment. This review

to a degree has progressed to explain the part of metformin movement on gluconeogenesis in hepatocytes. [7,8]

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 of drugs of diabetes.[9]

Diabetic treatment with metformin is related with decrease ingain of weight contrasted and insulin and sulfonylureas. Glucose is controlled better in weight gain instances. A review has shown that, on a ten year period of treatment, metformin treated patients acquired around 1 kilograms, glibenclamide treated patients acquired around 3 kilograms, insulin treated patients acquired six kg weight.[10]

Poly-Cystic Ovarian syndrome

Poly-cystic 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 a index of body mass over 25 for both infertile and anovulated 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 way of life change autonomous from drug treatment.

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 failure is seen in 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]

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]

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.

As a Adjuvant Treatment for Cancer

Examination proposes that metformin can work as valuable adjuvant specialist, especially in prostate also colorectal malignant growth. A quantity of studies recognized that every growth type is probably going to mirror the occurrence and socioeconomics of the illness, especially the probability of show with beginning phase sickness and an analysis of diabetes mellitus.An idea of randomized clinical preliminaries utilizing metformin as an adjuvant, alongwith the most grounded aiding proof inprostate alongwith colorectal malignant growth, especially who got treatment with revolutionary radiation therapy. [20]

The variety in the adjuvant impacts of metformin as indicated by type of cancercan be clarified by contrasts in patient qualities and growth science. Metformin impact on AMPK

flagging have been conjectured as a significant routeby which metformin applies upon the targets of malignancy impacts [21]. AMPK flagging dysregulation is additionally connected with metabolic disorder [22], a group of situations which incorporate raised blood glucose before meal, hyperlipidaemia, hypertension withobese condition [23]. Disorders related to metabolism is additionally seenbuilding 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; 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 part in controlling cell reactions in radiation therapy, [27] considers to xenograft models of rat recommend metformin, which can further develop growth oxygenation alongwith thusly radiations [28].

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 predispositionsrelatedto time [29]. Serious levels in variety among the aftereffects of researches was noticed for some results researched in a large portion undertypes of malignancy. Affectability investigations done were to intend and investigate potential explanations behind these to illuminate further observational alongwith clinical preliminary plan; notwithstanding, just few examinations were conceivable because of inadequate review digits. Both colorectal and prostate malignancy, overall impact amount seemed as a increment for examines alongwith followup of three years ,even more noteworthy, featuring about the significance of guaranteeing satisfactory span in following up for later investigations. Likenesses has been found among investigations of headache medicine, in which more prominent advantages has been seen having longer followup [30-32].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.

Past examinations have recommended that an analysis of diabetes mellitus adversely affects disease results [33,34]; in this manner, consideration of non- diabetes mellitusvictims in comparator gatherings would belittle 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.

Examination about metformin in the essential anticipation setting shows various difficulties, where the harmony between unfavourable impacts and advantages is probably going to be low good ,also hard to recognize in preliminaryclinicals on account of less occasion rate. Whereas the high level 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 forlong which would be enoughto arise helpful advantage. Accordingly, the adjuvant quality could generally be reasonable about researching of counter malignant growth impacts of metformin.

Lactic Acidosis

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]. Death rate in patients having metformin related lactic acidosis has all the earmarks of being ∼40% and furthermore gives off an impression of being related with cardiovascular breakdown [36,37].It was observed that out of all patients, only four didn't show other risk factors of lactic acidosis after metformin 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.

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 broadly held tested impression that lactic acidosis caused by metformin is wrongly strengthened. Lactic acidosis happens among non-diabetic victims in relationship with disease, malignant growth, disorders of liver, with kidney disappointment and also quite often a death harbinger except if the situation that is hidden is adjusted [38,39].Victims suffering from typeII diabetes, pace of lactic-acidosis accounted for [40],should be comparative among patientsusing metformin also in victimswho never used metformin.

Stacpoole [41] has proposed that casesabout metformin related lactic acidosis address "responsibility by relationship" alongwith phenformin. Stades et al. [37] ascribed several casesabout 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 about metformin, which is frequently a blameless spectator.The quantity of reported instances about metformin-related lactic acidosis is little if someone thinks about ways metformin is utilized [37]. This metformin have been utilized securely in victims with serious post drug effects (43–48) can be observed as proof about itsnot 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 with 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 about metformin related lactic acidosis, especially deadly types, which were likely unbrought about by the drug metformin.[49-58]

CONCLUSION

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 show not just that the medication can be utilized all the more generously as for renal capacity, yet that it could add to renal assurance. Information additionally demonstrate 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 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 load.

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.

Even though the utilization of utilization 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 have driven scientists to acknowledge the utilization of this medication.

REFERENCES

1. Scheen AJ, Paquot N. Metformin revisited: A critical review of the benefit–risk balance in at-risk patients with type 2 diabetes. Diabetes & metabolism. 2013 May 1;39(3):179-90.
2. Kirpichnikov D, McFarlane SI, Sowers JR. Metformin: an update. Annals of internal medicine. 2002 Jul 2;137(1):25-33.
3. Hundal RS, Inzucchi SE. Metformin. Drugs. 2003 Sep;63(18):1879-94.
4. Scarpello JH, Howlett HC. Metformin therapy and clinical uses. Diabetes and Vascular Disease Research. 2008 Sep;5(3):157-67.
5. Rafieian-Kopaei M, Baradaran A. Combination of metformin with other antioxidants may increase its renoprotective efficacy. Journal of renal injury prevention. 2013;2(2):35-6.
6. Rena G, Hardie DG, Pearson ER. The mechanisms of action of metformin. Diabetologia. 2017 Sep;60(9):1577-85.
7. Seo-Mayer PW, Thulin G, Zhang L, Alves DS, Ardito T, Kashgarian M, Caplan MJ. Preactivation of AMPK by metformin may ameliorate the epithelial cell damage caused by renal ischemia. American journal of physiology-renal physiology. 2011 Dec;301(6):F1346-57.
8. Sung JY, Choi HC. Metformin-induced AMP-activated protein kinase activation regulates phenylephrine-mediated contraction of rat aorta. Biochemical and biophysical research communications. 2012 May 11;421(3):599-604.
9. Rösen P, Wiernsperger NF. Metformin delays the manifestation of diabetes and vascular dysfunction in Goto–Kakizaki rats by reduction of mitochondrial oxidative stress. Diabetes/metabolism research and reviews. 2006 Jul;22(4):323-30.
10. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). The Lancet. 1998 Sep 12;352(9131):854-65.
11. Kidson W. Polycystic ovary syndrome: a new direction in treatment. Medical journal of Australia. 1998 Nov;169(10):537-40.
12. National Institute for Clinical Excellence. Clinical Guideline 11: Fertility: Assessment and Treatment for People with Fertility Problems. Nice; 2004.
13. Balen AH, Morley LC, Misso M, Franks S, Legro RS, Wijeyaratne CN, Stener-Victorin E, Fauser BC, Norman RJ, Teede H. The management of anovulatory infertility in women with polycystic ovary syndrome: an analysis of the evidence to support the development of global WHO guidance. Human reproduction update. 2016 Nov 20;22(6):687-708.
14. Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Consensus on infertility treatment related to polycystic ovary syndrome. Human reproduction. 2008 Mar 1;23(3):462-77.
15. Palomba S, Pasquali R, Orio Jr F, Nestler JE. Clomiphene citrate, metformin or both as first- step approach in treating anovulatory infertility in patients with polycystic ovary syndrome (PCOS): a systematic review of head- to- head randomized controlled studies and meta- analysis. Clinical endocrinology. 2009 Feb;70(2):311-21.
16. Al-Inany H, Johnson N. Drugs for anovulatory infertility in polycystic ovary syndrome.
17. Tang T, Lord JM, Norman RJ, Yasmin E, Balen AH. Insulin- sensitising drugs (metformin, rosiglitazone, pioglitazone, D- chiro- inositol) for women with

polycystic ovary syndrome, oligo amenorrhoea and subfertility. Cochrane Database of Systematic Reviews. 2012(5).
18. Radosh L. Drug treatments for polycystic ovary syndrome. American family physician. 2009 Apr 15;79(8):671-6.
19. Palomba S, Orio Jr F, Falbo A, Russo T, Tolino A, Zullo F. Clomiphene citrate versus metformin as first-line approach for the treatment of anovulation in infertile patients with polycystic ovary syndrome. The Journal of Clinical Endocrinology & Metabolism. 2007 Sep 1;92(9):3498-503.
20. Coyle C, Cafferty FH, Vale C, Langley RE. Metformin as an adjuvant treatment for cancer: a systematic review and meta-analysis. Annals of Oncology. 2016 Dec 1;27(12):2184-95.
21. Dowling RJ, Zakikhani M, Fantus IG, Pollak M, Sonenberg N. Metformin inhibits mammalian target of rapamycin–dependent translation initiation in breast cancer cells. Cancer research. 2007 Nov 15;67(22):10804-12.
22. Ruderman NB, Carling D, Prentki M, Cacicedo JM. AMPK, insulin resistance, and the metabolic syndrome. The Journal of clinical investigation. 2013 Jul 1;123(7):2764-72.
23. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, Fruchart JC, James WP, Loria CM, Smith Jr SC. Harmonizing the metabolic syndrome: a joint interim statement of the international diabetes federation task force on epidemiology and prevention; national heart, lung, and blood institute; American heart association; world heart federation; international atherosclerosis society; and international association for the study of obesity. Circulation. 2009 Oct 20;120(16):1640-5.
24. Giovannucci E. Metabolic syndrome, hyperinsulinemia, and colon cancer: a review. The American journal of clinical nutrition. 2007 Sep 1;86(3):836S-42S.
25. Shen Z, Ye Y, Bin L, Yin M, Yang X, Jiang K, Wang S. Metabolic syndrome is an important factor for the evolution of prognosis of colorectal cancer: survival, recurrence, and liver metastasis. The American Journal of Surgery. 2010 Jul 1;200(1):59-63.
26. Bosco C, Crawley D, Adolfsson J, Rudman S, Van Hemelrijck M. Quantifying the evidence for the risk of metabolic syndrome and its components following androgen deprivation therapy for prostate cancer: a meta-analysis. PloS one. 2015 Mar 20;10(3):e0117344.
27. Zannella VE, Cojocari D, Hilgendorf S, Vellanki RN, Chung S, Wouters BG, Koritzinsky M. AMPK regulates metabolism and survival in response to ionizing radiation. Radiotherapy and Oncology. 2011 Jun 1;99(3):293-9.
28. Zannella VE, Dal Pra A, Muaddi H, McKee TD, Stapleton S, Sykes J, Glicksman R, Chaib S, Zamiara P, Milosevic M, Wouters BG. Reprogramming metabolism with metformin improves tumor oxygenation and radiotherapy response. Clinical cancer research. 2013 Dec 15;19(24):6741-50.
29. Suissa S, Azoulay L. Metformin and the risk of cancer: time-related biases in observational studies. Diabetes care. 2012 Dec 1;35(12):2665-73.
30. Burn J, Gerdes AM, Macrae F, Mecklin JP, Moeslein G, Olschwang S, Eccles D, Evans DG, Maher ER, Bertario L, Bisgaard ML. Long-term effect of aspirin on cancer risk in carriers of hereditary colorectal cancer: an analysis from the CAPP2 randomised controlled trial. The Lancet. 2011 Dec 17;378(9809):2081-7.
31. Cook NR, Lee IM, Zhang SM, Moorthy MV, Buring JE. Alternate-day, low-dose aspirin and cancer risk: long-term observational follow-up of a randomized trial. Annals of internal medicine. 2013 Jul 16;159(2):77-85.

32. Rothwell PM, Wilson M, Elwin CE, Norrving B, Algra A, Warlow CP, Meade TW. Long-term effect of aspirin on colorectal cancer incidence and mortality: 20-year follow-up of five randomised trials. The Lancet. 2010 Nov 20;376(9754):1741-50.
33. Jeon JY, Jeong DH, Park MG, Lee JW, Chu SH, Park JH, Lee MK, Sato K, Ligibel JA, Meyerhardt JA, Kim NK. Impact of diabetes on oncologic outcome of colorectal cancer patients: colon vs. rectal cancer. PloS one. 2013 Feb 6;8(2):e55196.
34. Oh JJ, Hong SK, Lee S, Sohn SJ, Lee SE. Diabetes mellitus is associated with short prostate-specific antigen doubling time after radical prostatectomy. International urology and nephrology. 2013 Feb 1;45(1):121-7.
35. Bodmer M, Meier C, Krähenbühl S, Jick SS, Meier CR. Long-term metformin use is associated with decreased risk of breast cancer. Diabetes care. 2010 Jun 1;33(6):1304-8.
36. Misbin RI, Green L, Stadel BV, Gueriguian JL, Gubbi A, Fleming GA. Lactic acidosis in patients with diabetes treated with metformin. New England Journal of Medicine. 1998 Jan 22;338(4):265-6.
37. Stades AM, Heikens JT, Erkelens DW, Holleman F, Hoekstra JB. Metformin and lactic acidosis: cause or coincidence? A review of case reports. Journal of internal medicine. 2004 Feb;255(2):179-87.
38. Stacpoole PW, Harman EM, Curry SH, Baumgartner TG, Misbin RI. Treatment of lactic acidosis with dichloroacetate. New England Journal of Medicine. 1983 Aug 18;309(7):390-6.
39. Stacpoole PW, Wright EC, Baumgartner TG, Bersin RM, Buchalter S, Curry SH, Duncan C, Harman EM, Henderson GN, Jenkinson S, Lachin JM. Natural history and course of acquired lactic acidosis in adults. The American journal of medicine. 1994 Jul 1;97(1):47-54.
40. . Brown JB, Pedula K, Barzilay J, Herson MK, Latare P. Lactic acidosis rates in type 2 diabetes. Diabetes care. 1998 Oct 1;21(10):1659-63.
41. . Brown JB, Pedula K, Barzilay J, Herson MK, Latare P. Lactic acidosis rates in type 2 diabetes. Diabetes care. 1998 Oct 1;21(10):1659-63.
42. . Lalau JD, Race JM. Lactic acidosis in metformin-treated patients. Drug safety. 1999 Apr;20(4):377-84.
43. Sulkin TV, Bosman D, Krentz AJ. Contraindications to metformin therapy in patients with NIDDM. Diabetes care. 1997 Jun 1;20(6):925-8.
44. . Evans JM, Donnelly LA, Emslie-Smith AM, Alessi DR, Morris AD. Metformin and reduced risk of cancer in diabetic patients. Bmj. 2005 Jun 2;330(7503):1304-5.
45. Horlen C, Malone R, Bryant B, Dennis B, Carey T, Pignone M, Rothman R. Frequency of inappropriate metformin prescriptions. Jama. 2002 May 15;287(19):2504-5.
46. Holstein A, Nahrwold D, Hinze S, Egberts EH. Contra- indications to metformin therapy are largely disregarded. Diabetic Medicine. 1999 Aug;16(8):692-6.
47. Rachmani R, Slavachevski I, Levi Z, Zadok BS, Kedar Y, Ravid M. Metformin in patients with type 2 diabetes mellitus: reconsideration of traditional contraindications. European Journal of Internal Medicine. 2002 Oct 1;13(7):428-33.
48. . Masoudi FA, Wang Y, Inzucchi SE, Setaro JF, Havranek EP, Foody JM, Krumholz HM. Metformin and thiazolidinedione use in Medicare patients with heart failure. Jama. 2003 Jul 2;290(1):81-5.
49. Ashfaque, Aaliya Rukhsar Mohammad, Najnin Khanam, Farhan Khan, Rutuj Narendra Waghmare, and Shobha Kanhaiyalal Joshi. “Assessment of Self-Care Practices among Type 2 Diabetes Patients at a Tertiary Care Hospital - A Cross-Sectional Study.” JOURNAL OF EVOLUTION OF MEDICAL AND DENTAL

SCIENCES-JEMDS 9, no. 36 (September 7, 2020): 2630–35. https://doi.org/10.14260/jemds/2020/572.
50. Ashtankar, Poonam, V, and Punam Sawarkar. “Role of Panchatikta Panchaprasutik Niruha Vasti in Prediabetes A Case Report.” INTERNATIONAL JOURNAL OF AYURVEDIC MEDICINE 11, no. 3 (September 2020): 588–93.
51. Belsare, Anuja, Gaurav Sawarkar, and Pratiksha Mahure. “An Observational Study Protocol For The Prevalence Of Non-Insulin Dependent Diabetes Mellitus In Different Types Of Prakruti In Wardha City.” International Journal Of Modern Agriculture 9, No. 3 (2020): 96–99.
52. Inamdar, Saunitra A., Himanshi Agarwal, Sourya Acharya, and Anil Inamdar. “Coexistence of Hypertriglyceredemia and Hypercholesterolemia with Gestational Diabetes Mellitus in Pregnancy: A Case Report.” MEDICAL SCIENCE 24, no. 102 (April 2020): 594–98.
53. Jankar, Jayshri Sadashiv, Kumud Namdeorao Harley, Kanchan Manoharrao Mohod, and Vijay Yashwantrao Babar. “Association of Urinary Albumin with HbA1c Levels in Subjects of Type 2 Diabetes Mellitus in Central India.” JOURNAL OF EVOLUTION OF MEDICAL AND DENTAL SCIENCES-JEMDS 9, no. 52 (December 28, 2020): 3921–25. https://doi.org/10.14260/jemds/2020/859.
54. Kamble, T. K., Ankita Kapse, Sunil Kumar, Sourya Acharya, and Aiswarya Ghule. “Study of Myocardial Performance Index in Prediabetes and Its Correlation with Other Cardiovascular Risk Factors.” JOURNAL OF EVOLUTION OF MEDICAL AND DENTAL SCIENCES-JEMDS 9, no. 10 (March 9, 2020): 721–25. https://doi.org/10.14260/jemds/2020/157.
55. Thorat, Vaibhav, Imranali M. Khan, and Sakshi Gaikwad. “Platelet Rich Fibrin Matrix the Cost Effective Way to Treat Trophic Ulcer in Diabetes: A Pilot Study.” MEDICAL SCIENCE 24, no. 104 (August 2020): 2752–59.
56. Unnikrishnan, B., P. Rathi, S. K. Bhat, P. H. Nayak, N. Ravishankar, A. Singh, and O. Praveen. “Risk Factors of Gestational Diabetes Mellitus: A Hospital-Based Pair-Matched Case-Control Study in Coastal South India.” SAJOG-SOUTH AFRICAN JOURNAL OF OBSTETRICS AND GYNAECOLOGY 26, no. 1 (June 2020): 13–17. https://doi.org/10.7196/SAJOG.2020.v26i1.1518.
57. Rathi, Nikhil, Bharati Taksande, and Sunil Kumar. “Nerve Conduction Studies of Peripheral Motor and Sensory Nerves in the Subjects With Prediabetes.” JOURNAL OF ENDOCRINOLOGY AND METABOLISM 9, no. 5 (October 2019): 147–50. https://doi.org/10.14740/jem602.
58. Ray, Kausik K., Helen M. Colhoun, Michael Szarek, Marie Baccara-Dinet, Deepak L. Bhatt, Vera A. Bittner, Andrzej J. Budaj, et al. “Effects of Alirocumab on Cardiovascular and Metabolic Outcomes after Acute Coronary Syndrome in Patients with or without Diabetes: A Prespecified Analysis of the ODYSSEY OUTCOMES Randomised Controlled Trial.” LANCET DIABETES & ENDOCRINOLOGY 7, no. 8 (August 2019): 618–28. https://doi.org/10.1016/S2213-8587(19)30158-5.