Volume 17 Issue 17
Originally issued as B3

Global Journal of Medical Research: B
Pharma, Drug Discovery, Toxicology & Medicine
Volume 17 Issue 3 Version 1.0 Year 2017
Type: Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals Inc. (USA)
Online ISSN: 2249-4618 & Print ISSN: 0975-5888

Metformin: A Unique Herbal Origin Medication

By Nadin Yousef, Farah Yousef, Oussama Mansour & Jehad Herbali
Damascus University

Abstract- Many oral anti-hyperglycemic agents have been used for treatment of Type II diabetes (TY2D), yet Metformin, the only compound remained of biguanide derivates, continued to be used in this treatment. Its mechanism of action and pharmacokinetics are unique and significant. It has low side effects and no adverse incidences with healthy heart and kidney T2D, compared with its family group members. The previous properties made metformin tops the oral anti hyperglycemic agents list recommended from FDA in TY2D therapy. In this review paper, we aimed to point at bi-guanide development through time as glucose lowering agents, and show the magnificent characteristics of dimethylbiguanide; metformin.

GJMR-B Classification: *NLMC Code: QV 767*

Strictly as per the compliance and regulations of:

© 2017. Nadin Yousef, Farah Yousef, Oussama Mansour & Jehad Herbali. This is a research/review paper, distributed under the terms of the Creative Commons Attribution-Noncommercial 3.0 Unported License http://creativecommons.org/licenses/by-nc/3.0/), permitting all non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

Metformin: A Unique Herbal Origin Medication

Nadin Yousef [α], Farah Yousef [σ], Oussama Mansour [ρ] & Jehad Herbali [ω]

Abstract- **Many oral anti-hyperglycemic agents have been used for treatment of Type II diabetes (TY2D), yet Metformin, the only compound remained of biguanide derivates, continued to be used in this treatment. Its mechanism of action and pharmacokinetics are unique and significant. It has low side effects and no adverse incidences with healthy heart and kidney T2D, compared with its family group members. The previous properties made metformin tops the oral anti hyperglycemic agents list recommended from FDA in TY2D therapy. In this review paper, we aimed to point at bi-guanide development through time as glucose lowering agents, and show the magnificent characteristics of dimethylbiguanide; metformin.**

I. Introduction

a) Origin Background

In 1920s, guanidine based compounds were firstly known with their efficacy as anti-hyperglycemic agents [1], yet their origins go back to 1600s, when a plant; Galega officinalis, was commonly used in European Folklore to decrease the symptoms of what it's known today as type II diabetes (TY2D).[2] [3]

Although this plant, also known as Goat's Rue or French Lilac, was found, in late 1800s, to be full of guanidine and galagine; isoamylene guanidine,[4] [5] [6] [7] however the efficacy of guanidine to lower blood glucose levels was not proven in animals till 1918.

This invention struggled some challenges as the toxicity of guanidine decreased its chance as a potential hypoglycemic drug, and the discovery of safer guanidine based structure compounds was somehow not succeeded by scientists, as well. Moreover, that the era of insulin discovery and availability by that time downplayed guanidine effectiveness role in diabetes treatment.[]

Through what the world had witnessed of crises in 1900s, Researches did not stop investigating G. officinalis; there were still eyes on galagine as safer anti hyperglycemic agent than guanidine.

However, that was not for too long with the presence of diguanide compounds; decamethylene diguanide (Synthalin A®) and dodecamethylene diguanide (Synthalin B®) in the clinical use by the same period of time.

These diguanide compounds were more tolerated than guanidine compounds, but their hepatic toxicity reports in 1930s were the cause of not prescribing them any longer by medical professionals.[8]

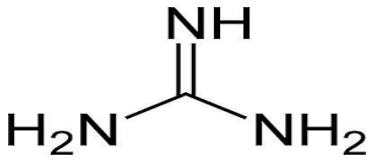
Although many guanidine compounds were synthesized in 1929, but biguanide derivates did not see the light till the later of 1950s. Phenoformin was discovered by Urgan and Shapiro and it was introduced to the medical usage in 1958 with DPI®.[9] While Buformin was discovered by Mehnert.[10]

In spite of these two proved greater efficacy than our unique compound, the lactic acidosis incidences that follow the use of them resulted in withdrawing them from the market in 1970s. [11] [12] [13]

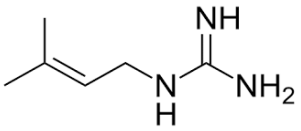
Metformin; Dimethyl-biguanide, the only bi-guanide remained in TY2D remedy, was developed by Jean Sterne in France. His results were published in 1957 and he was the one who named metformin as "Glucophage"; glucose eater.[14] [15] Yet, American Food and Drugs Administration did not approve on metformin usage in the U.S market till 1995. [16]

b) Bi-guanide chemical development

Guanidine and galagine structures are shown in fig 1. Di-guanide compounds are presented in fig 2, and Biguanide compounds have the general structure shown in fig 3. These compounds' structures are shown in fig 4.[17] Their chemical and physical properties are shown in Table 1.



Guanidine



Galagine

Figure 1: Guanidine and Galagine structures

Author σ: Damascus University. e-mail: farahyousef90@yahoo.com

© 2017 Global Journals Inc. (US)

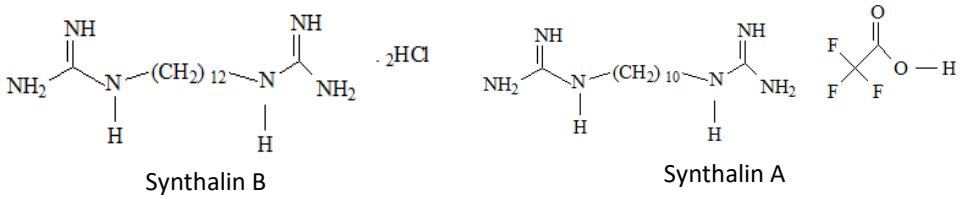


Figure 2: Di-guanide derivates' structures

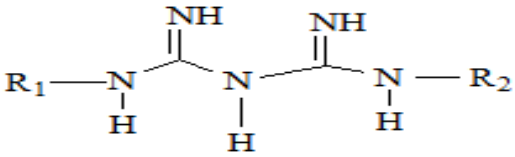


Figure 3: Biguanide derivates' general structure

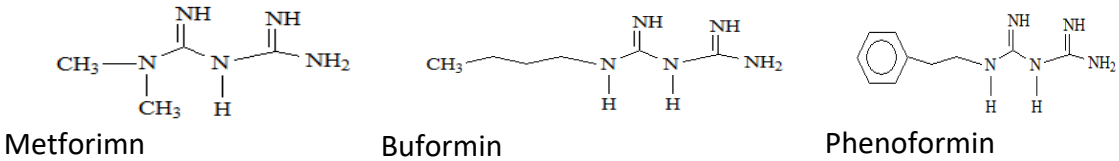


Figure 4: Biguanides' compounds

Table 1: Chemical properties of biguanide derivates [18]

Compound Name	M. Weight	Log P	pK_a	Hydrogen bound Donner count	Hydrogen bound acceptor count	Dosage mg\day	Rel. potency
Synthalin A	370.23	N\A	N\A	5	7	N\A	N\A
Synthalin B	357.368	N\A	N\A	4	4	N\A	N\A
Buformin	157.221	-1.2	N\A	3	1	N\A	N\A
Phenoformin	241.723	-0.83	N\A	4	1	N\A	N\A
Metformin	129.167	-0.5	12.4	3	1	500\3	N\A

Metformin is the safest biguanide derivates in use by TY2D patients.[19] As can be inferred from metformin structure, it is a bi-guanide derivate, no $(CH_2)_n$ chain separates between the two guanidine groups. R_1, R_2 are small alkyl groups ($-CH_3$).

On the other hand, di-guanide derivates have been withdrawn from the market due to their adverse to toxic effects; Synthalins for their hepato-toxicity, while phenoformin and buformin; bi-guanide derivates, for their lactic acidosis incidences. [16]

As can be seen from their structures, having $(-CH_2-)_{10}$ chain, $(-CH_2-)_{12}$ chain separating between two guanidine groups as there are respectively in Synthalin A and Synthalin B, or $(Ar-CH_2-CH_2-)$ moiety as it is in phenoformin, might be responsible for the undesirable effects of these compounds. However, their anti-hyperglycemic efficacy were stronger than metformin.

This can indicate an inquiry that does shortening $(CH_2)_n$; $n<10$, or having other small or cyclic moieties on the both terminal NH_2 can take a part in these compound efficacy or decrease the adverse effects biguanide compounds struggled with?! This hypothesis is still in question.

Recent research has proven that a number of other biguanide hydrochloride derivates also have anti diabetic activity. One of them, actually has a di-oxymethyl benzene moity in its chemical Skelton. Structures of these compounds are shown in fig (5).[20]

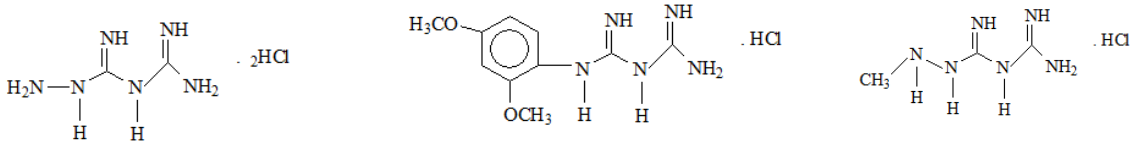


Figure 5: Biguanide derivates work as anti diabetic agents

© 2017 Global Journals Inc. (US)

c) *Metformin Synthesis*

Shapiro had prepared metformin from the reaction between dimethylamine hydrochloride and dicyano diamide at 120-140 °C in 4 hrs time with 69% yield. [21]

New route was used in this synthesis. This ecologically safe protocol using microwaves; 540W, shortens the reaction time; 5mins, reduce the amount used of solvents, to obtain a clean product with yield of 92% by optimum use of energy and tiny amounts of reacted materials. Fig (6) [22]

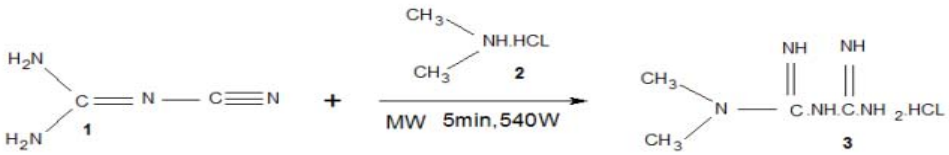


Figure 6: New synthesis route for metformin

d) *Metformin unique Characteristics*

i. *Pharmacodynamics*

According to American Diabetes Association, metformin is the first-line drug for treatment of T2D patients in the world. Metformin can be considered Sugar Regulator rather than anti-hyperglycemic agent.[23] [24]

Its mechanism of action does not differ from phenoformin's. They both increase AMPK activation in hepatic cells.[5] [25] [26] Recent research demonstrates that their pharmacodynamics play deeper role interacting with cellular bioactivity. they interact with Hepatic Mitochondrial Respiratory Chain Complex 1(H^+ giant pump). [27] [28] [29]

This results in decreasing the cellular production of ATP.[30] In both ways, Energy sources in hepatic cells are reduced resulting in enhancing insulin receptor sensitivity toward insulin.[31]

That makes the main peripheral targeted cells; skeletal muscle, and hepatic cells, stop glycogenesis operation and produce more insulin receptors and Glucose Transporter 4 (GLUT-4) to augment glucose inwardly transportation.[32] [33] [34] [35]

ii. *Pharmacokinetics*

No information was provided about biguanide derivates' pharmacokinetics but for Metformin. It is 50-60 % absorbed after an oral single dosage of (500. 850, 1000) mg. Its protein binding percentage is negligible. It is eliminated unchanged in the urine.[36] [37] Its half-life is 6.2 hours with duration of action 8-12 hours.

iii. *Superiority*

Hundreds of efficacy studies verified metformin superiority to the rest of his family members, and other chemical groups, used in Type II diabetes therapy.[38] [39] Likewise, toxicology experiments affirmed its narrow toxicity margin. Metformin advantage\ risk scale brought it to be the first drug in the guideline of initial remedy of Type II diabetes. [40] [41]

As glucose blood levels become uncontrollable by time due to disease progression in TY2D and the life styles in many communities facilitates in this falling back, many oral anti hyperglycemic agent combinations with metformin presented in the drug market. [42] [43] [44]

Metformin combination with Sulfonyl-urea is very common. In fact, this double combination has proven more efficacy than if each drug was solely taken. Glucovans ® is the trade name of metformin and glyburide combination. [45] [46]

Above all that, this ancient-modern small molecule can be used in adolescents and childhood, as TY2D since 1990 started to be caused not only in adults but also in children. [47] [48]

e) *Side Effects and Other benefits*

Metformin has no significant side effects with its labeled dosage.[49] The most frequently reported adverse events were digestive disturbance such as stomach ache, diarrhea, and vomiting. It also may cause headaches.

However, these undesired effects can be reduced when metformin is taken during meals, or as extended release pharmaceutical forms; metformin XR. [50] [51] Furthermore, metformin reduces mortality compared to other anti-diabetic agents.[52]

This magical bi-guanide compound distinguished itself from other oral anti hyperglycemic agents side effects. Its usage does not lead to clinical hypoglycemia, lactic acidosis, or changes in physical examinations. Yet, rare lactic acidosis reported in some cases where over dosage was taken. [53] [54]

In other words, Metformin magnificent side effect in its modest losing weight assistant made it likable to be prescribed by medical professions for obese TY2D patients.[55] [56] [57]

This significant usage was especially observed in obese children with or without Type II diabetes (TY2D) compared to diet. Proposed mechanism of this effect is by reducing glucose absorption levels. [58] [59] [60] [61] [62]

This herbal origin drug is also used in poly cystic ovary. [63] [64] Latest researches deepens its effectiveness in Cancer treatment, as well.[65] [66] [67] Besides to that, metformin has proven anti stress efficacy that led it to be used in inflammatory cases, and anti-aging factor, too.[68]

© 2017 Global Journals Inc. (US)

Furthermore, clinical studies verified its role in decreasing cardiovascular mortality by decreasing cholesterol blood levels and macro vascular cells' formation.[20] [69] [70]

Metformin proved its positive role in metabolic syndrome patients, as well as it enhances neuron system health.[71] [72] [73]

i. *Contraindications*

Heart failure is considered a potential contraindication for metformin usage in T2D treatment. Though lactic acidosis incidences are rare with metformin, yet this metabolic disturbance might be fatal in heart failure patients as it leads to hypo-perfusion.[74] [75] Despite this potential risk, yet FDA did not announce heart failure as contraindication for metformin.[76]

Because metformin is eliminated unchanged in the urine, renal failure is another metformin contraindication. However, the level of renal dysfunction was not determined in which to be considered risky for metformin usage or not to avoid lactic acidosis incidences.[77] [78] [79]

ii. *Drug Interactions*

On the long term of taking, Metformin decreases the absorption of vitamin B_{12}.[80] [81] Renal eliminated drugs such as digoxin, ranitidine, trimethoprime and many others also has interaction with metformin way of elimination.

iii. *Prescriptions in the Market*

Though metformin was shadowed from the time it was synthesized; 1920s, passing by its development in 1950s, till it was approved by FDA in 1995; nowadays, Metformin is categorized as essential drug in the World Health Organization's (WHO) lists for TY2D treatment. [82]

Bristol-Myers Squibb Company ; an American pharmaceutical global company, got the protection patent of marketing metformin under the trade name Glucophage till 2002.[83] Its prescriptions extended 50 million filled in the US alone, and Bristol-Myers Squibb earnings of this investment reached peak sales of US$2.7 billion in 2001. [84]

By the time the protection patent expired, many companies such as Lubrizol, Zydus Pharmaceuticals and others compete for marketing approved generics such as Glucophage, Glucophage XR, Riomet, Fortamet, Glumetza, Jentadueto, JANUMET® XR, Synjardy®, INVOKAMET™.

Due to this strong market completion, It is expected that metformin market value increase 2.1% in 2021 compared with its market value in 2014. It is estimated that metformin market value in 2014 was 660 million USD. As global statics indicate, this might reach 720 million USD in 2021.

II. Conclusion

We tried in this review to shed light on biguanide discovery history and the chemical differences among this group compounds that are in a way or another responsible of their characteristics.

However, We look forward for more researches to be done in this field in aim to have as modified structures as it can be done to have better anti-hyperglycemic agents with less side effects and proven efficacy.

References Références Referencias

1. Mori A, Cohen BD, Lowenthal A (eds). Guanidines – historical, biological, biochemical and clinical aspects of the naturally occurring guanidine compounds. London: Plenum Press, 1985.
2. Bailey CJ, Day C. Traditional plant medicines as treatments for diabetes. Diabetes Care 1989; 12: 553–564.
3. Bailey CJ. Biguanides and NIDDM. Diabetes Care 1992; 15: 755–772.
4. Leclerc H. Le galega. Paris: Presse Med, 22 Dec 1928.
5. British Herbal Pharmacopoeia. Keighley, UK: British Herbal Medicine Association, 1976.
6. Duke JA. Handbook of medicinal herbs, 2nd edn. Boca Raton, Florida: CRC Press, 2002; 337.
7. Muller H, Rheinwein H. Pharmacology of galegin. Arch Exp Path Pharmacol 1927; 125: 212–228.
8. Bischoff F.; Sahyun M.; Long M, Guanidine Structure and Hypoglycemia, 2017, http://www.jbc.org
9. Ungar G, Freedman L, Shapiro SL. Pharmacological studies of a new oral hypoglycaemic drug. Proc Soc Exp Biol Med 1957; 100: 190–192. 21.
10. Mehnert H, Seitz W. Weitere Ergebnisse der diabetesbehandlung mit blutzuckersenkenden biguaniden. Munch Med Wschr 1958; 100: 1849–1851
11. Lactic Acidosis with Recovery In Diabetes Mellitus On Phenformin Therapy Jorge H. Mestman, M.D., Dean S. Pocock, M.D., and Arthur Kirchner, M.D., Los Angeles, Califrina Medicine, SEPTEMBER 1969 * II 3, 1969.
12. William C. Gong; Donald B. Kato, Phenformin Induced Lactic Acidosis, Drag Intelligence and Clinical Pharmacy VOL 9: 236-240.
13. Nattrass, M.; Alberti, K.G. Biguanides. Diabetologia 1978, 14, 71–74.
14. Sterne J. Pharmacology and mode of action of the hypoglycaemic guanidine derivatives. In Oral hypoglycaemic agents. Campbell GD (ed). London: Academic Press, 1969; 193–245.
15. Hermann LS. Metformin: a review of history, pharmacodynamics and therapy. Diabetes Metab Rev 1979; 5: 233–245.
16. Bailey CJ, Turner RC. Metformin. N Engl J Med 1996; 334: 574–579.
17. Meiter ch., Bodmer m, Metformin, sulfonylureas, or other antidiabetes drugs and the risk of lactic

© 2017 Global Journals Inc. (US)

acidosis or hypoglycemia, Diabetes care, 2008, Vol 31, 2086-2091.
18. https://pubchem.ncbi.nlm.nih.gov/
19. American Diabetes Association. Implication of the united kingdome prospective diabetes study. Diabetes Care 2002; 25: 52832.
20. El-Bayouki Kh.; Abdel-Rahman R., Synthesis and evaluation of 1- substituted- biguanide derivates as anti-diabetic agents for type II diabetes Insulin Resistant, Drug Res, 2016, Vol 66, p: 1-7.
21. Shapiro, S. L.; Parrino, V. A.; Freedman, L. J. Am. Chem. Soc., 1959, 81, 3728.
22. Shalmalshi A, New Route to Metformin Hydrochloride (,-dimethylimidodicarbonimidic diamide hydrochloride) Synthesis, Molbank, 2008, http://www.mdpi.org/molbank/molbank2008/m564.htm.
23. Scarpello J.; Howllet H., Metformin therapy and clinical uses, Review, 2008, Vol: 5. P: 157-167.
24. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycemia in type 2 diabetes: A patient centered approach: Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2012; 35: 136479.
25. Nicolas M.; Michael F.; Hirshman, Metformin Increases AMP-Activated Protein Kinase Activity in Skeletal Muscle of Subjects with Type 2, Diabetes, DIABETES, 2002, Vol 51, p: 2074-2081.
26. Zang M, Zuccollo A, Hou X, Nagata D, Walsh K, Herscovitz H, et al. AMPactivated protein kinase is required for the lipidlowering effect of metformin in insulinresistant human HepG2 cells. J Biol Chem 2004; 279: 47898905.
27. El-Mir, M.Y.; Nogueira, V.; Fontaine, E.; Averet, N.; Rigoulet, M.; Leverve, X. Dimethylbiguanide inhibits cell respiration via an indirect effect targeted on the respiratory chain complex i. J. Biol. Chem. 2000, 275, 223–228. 11.
28. Emami Riedmaier, A.; Fisel, P.; Nies, A.T.; Schaeffeler, E.; Schwab, M. Metformin and cancer: From the old medicine cabinet to pharmacological pitfalls and prospects. Trends Pharmacol. Sci. 2013, 34, 126–135.
29. Leverve XM, Guigas B, Detaille D, Batandier C, Koceir EA, Chauvin C, et al. Mitochondrial metabolism and type2 diabetes: A specific target of metformin. Diabetes Metab 2003; 29: 6S8894.
30. Halestrap A.; Owen m., Evidence that metformin exerts its anti-diabetic effects through inhibition of complex 1 of the mitochondrial respiratory chain, Biochemical society, 2000, p: 607-614.
31. A specific target of metformin. Diabetes Metab 2003; 29: 6S8894. 14. Miller RA, Chu Q, Xie J, Foretz M, Viollet B, Birnbaum MJ. Biguanides suppress hepatic glucagon signalling by decreasing production of cyclic AMP. Nature 2013; 494: 25660.
32. Viollet B, Guigas B, Sanz Garcia N, Leclerc J, Foretz M, Andreelli F. Cellular and molecular mechanisms of metformin: an overview. Clin Sci (Lond) 2012; 122: 253-70.
33. Caton PW, Nayuni NK, Kieswich J, Khan NQ, Yaqoob MM, Corder R. Metformin suppresses hepatic gluconeogenesis through induction of SIRT1 and GCN5. J Endocrinol 2010;205:97106.
34. He L, Sabet A, Djedjos S, et al. Metformin and insulin suppress hepatic gluconeogenesis through phosphorylation of CREB binding protein. Cell. 2009; 137: 635–46.
35. Foretz M, Hébrard S, Leclerc J, Zarrinpashneh E, Soty M, Mithieux G, et al. Metformin inhibits hepatic gluconeogenesis in mice independently of the LKB1/AMPK pathway via a decrease in hepatic energy state. J Clin Invest 2010; 120: 235569.
36. Scheen AJ. Clinical pharmacokinetics of metformin. Clin Pharmacokinet 1996; 30: 359-71.
37. J, Arora M, Day RO, Doogue MP, Duong JK, et al. Clinical pharmacokinetics of metformin. Clin Pharmacokinet 2011; 50: 81-98.
38. American Diabetes Association: Summary of revisions to the 2011 clinical practice recommendations. Diabetes Care 2011, 34(Suppl 1): S3.
39. Turner RC, Cull CA, Frighi V, Holman RR: Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes: progressive requirement for multiple therapies (UKPDS 49). JAMA 1999, 281: 2005–2012.
40. Howlett HCS, Bailey CJ. A risk–benefit assessment of metformin in type 2 diabetes mellitus. Drug Safety 1999; 20: 489–503.
41. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycaemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia 2012; 55: 1577-96.
42. Bennett WL, Maruthur NM, Singh S, Segal JB, Wilson LM, Chatterjee R, et al. Comparative effectiveness and safety of medications for type 2 diabetes: an update including new drugs and 2-drug combinations. Ann Intern Med 2011; 154: 602-13.
43. Raskin P. Oral combination therapy: repaglinide plus metformin for treatment of type 2 diabetes. Diabetes Obes Metab. 2008; 10: 1167–77.
44. Charbonnel B, Karasik A, Liu J, Wu M, Meininger G; Sitagliptin Study 020 Group. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin added to ongoing metformin therapy in patients with type 2

© 2017 Global Journals Inc. (US)

diabetes inadequately controlled with metformin alone. Diabetes Care. 2006; 29: 2638–43.
45. Gerich J, Raskin P, Jean-Louis L, et al: PRESERVE-beta: two-year efficacy and safety of initial combination therapy with nateglinide or glyburide plus metformin. Diabetes Care 2005, 28: 2093–2099.
46. González-Ortiza M, Guerrero-Romero J, Violante-Ortiz R, et al: Efficacy of glimepiride/metformin combination versus glibenclamide/metformin in patients with uncontrolled type 2 diabetes mellitus. J Diabetes Complications 2009, 23: 376–379.
47. Tock L, Dˆamaso A, de Piano A, Carnier J, et al: Long-Term Effects of metformin and lifestyle modification on nonalcoholic fatty liver disease obese adolescents. J Obes 2010, 831901: 6. Article ID 831901.
48. Park M, Kinra S, Ward K, White B, Viner R: Metformin for obesity in children and adolescents: a systematic review. Diabetes Care 2009, 32: 1743–1745.
49. Blonde L, Dailey GE, Jabbour SA, Reasner CA, Mills DJ. Gastrointestinal tolerability of extended-release metformin tablets compared to immediaterelease metformin tablets: results of a retrospective cohort study. Curr Med Res Opin. 2004; 20: 565–72.
50. Levy J, Cobas RA, Gomes MB: Assessment of efficacy and tolerability of once daily extended release metformin in patients with type 2 diabetes mellitus. Diabetol Metab Syndr 2010, 2: 16.
51. Raz I, Delaet I, Goyvaerts H, et al: Safety and efficacy of novel extended release formulation of metformin in patients with type 2 diabetes. Diabetes 2000, 49(Suppl 1): A363
52. Johnson JA, Majumdar SR, Simpson SH, et al: Decreased mortality associated with the use of metformin compared with sulfonylurea Monotherapy in type 2 diabetes. Diabetes Care 2002, 25: 2244–2248.
53. Scheen A; Paquot N., Metformin revisited: a critical review of the benefit/risk balance in “at risk” patients with type 2 diabetes, Diabetes & Metabolism, 1-30.
54. Hulisz DT, Bonfiglio MF, Murray RD: Metformin-associated lactic acidosis. J Am Board Fam Pract 1998, 11: 233–236.
55. 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). Lancet 1998; 352: 854–865.
56. Prospective Diabetes Study (UKPDS) Group: Effect of intensive blood glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 1998, 352(9131): 854–865.
57. Giugliano D, Quatraro A, Consoli G, et al: Metformin for obese, insulintreated diabetic patients: improvement in glycaemic control and reduction of metabolic risk factors. Eur J Clin Pharmacol 1993, 44: 107–112.
58. Vella S, Buetow L, Royle P, et al: The use of metformin in type 1 diabetes: a systematic review of efficacy. Diabetologia 2010, 53(5): 809–820.
59. Abdelghaffar S, Attia AM: Metformin added to insulin therapy for type 1 diabetes mellitus in adolescents. Cochrane Database Syst Rev 2009, (Issue 1):CD006691.
60. Wiegand S, Maikowski U, Blankenstein O, Bierbermann H, Tarnow P, Grutes A: Type 2 diabetes and impaired glucose tolerance in European children and adolescents with obesity- a problem that is no longer restrited to minority groups. Eur J Endocrinol 2004, 151: 199–206.
61. Pinhas-Hamiel O, Zeitler P: Clinical presentation and treatment of type 2 diabetes in children. Pediatr Diabetes 2007, 8(Suppl. 9): 16–27.
62. Jones KL, Arslanian S, Peterokova VA, Park JS, Tomlinson MJ: Effect of metformin in pediatric patients with type 2 diabetes: a randomized controlled trial. Diabetes Care 2002, 25: 89–94.
63. Palomba S, Falbo A, Zullo F, Orio F Jr. Evidence based and potential benefits of metformin in the polycystic ovary syndrome: A comprehensive review. Endocr Rev 2009; 30: 150.
64. Balasubramanyam M. Metformin: Nature’s gift that keeps on giving more!. J Obes Metab Res 2014; 1: 118-20.
65. Anisimov VN. Metformin: Do we finally have an antiaging drug? Cell Cycle 2013; 12: 34839.
66. Yin M, Zhou J, Gorak EJ, Quddus F. Metformin is associated with survival benefit in cancer patients with concurrent type 2 diabetes: A systematic review and metaanalysis. Oncologist 2013; 18: 124855.
67. Hatoum D.; McGowan e., Recent Advances in the Use of Metformin: Can Treating Diabetes Prevent Breast Cancer?, BioMed Research International Volume 2015: 1-14.
68. Aldea M, Craciun L, Tomuleasa C, Berindan Neagoe I, Kacso G, Florian IS, et al. Repositioning metformin in cancer: Genetics, drug targets, and new ways of delivery. Tumour Biol 2014,10.1007/s 1327701416768. http://link.springer.com/article/10. 1007%2Fs1327 7014 1 6768.
69. Krempf M, Parhofer KG, Steg G, et al: National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the NationalCholesterol Education Program (NCEP) Expert Panel on Detection. Circulation 2002, 106: 3143–3421.
70. Kooy A, de Jager J, Lehert P, et al: Long-term effects of metformin on metabolism and

© 2017 Global Journals Inc. (US)

microvascular and macrovascular disease in patients with type 2 diabetes mellitus. Arch Intern Med 2009, 169: 616–625.
71. Vitale C, Mercuro G, Cornoldi A, Fini M, et al: Metformin improves endothelial function in patients with metabolic syndrome. J Intern Med 2005, 258: 250–256.
72. Spasic MR, Callaerts P, Norga KK: AMP-Activated Protein Kinase (AMPK) Molecular Crossroad for Metabolic Control and Survival of Neurons. Neuroscientist 2009, 15(4): 309–316.
73. Van der Heide LP, Ramakers GM, Smidt MP: Insulin signaling in the central nervous system: learning to survive. Prog Neurobiol 2006, 79: 205–221.
74. Sulkin TV, Bosman D, Krentz A. Contraindications to metformin therapy in patients with NIDDM. Diabetes Care. 1997; 20: 925–9.
75. Evans JM, Ogston SA, Emslie-Smith A, Morris AD: Risk of mortality and adverse cardiovascular outcomes in type 2 diabetes: a comparison of patients treated with sulfonylureas and metformin. Diabetologia 2006, 49: 930–936.
76. Food and Drug Administration. Product label approval: metformin. 2006. http://packageinserts.bms.com/pi/piglucophage.pdf
77. Calabrese AT, Coley KC, Da Pos SV, Swanson D, Rao RH. Evaluation of prescribing practices: risk of lactic acidosis with metformin therapy. Arch Intern Med. 2002; 162: 434–7.
78. Lipska KJ, Bailey CJ, Inzucchi SE: Use of metformin in the setting of mild-to-moderate renal insufficiency. Diabetes Care 2011, 34(6): 1431–1437.
79. Frid A, Sterner GN, Londahl M, et al: Novel assay of metformin levels in patients with type 2 diabetes mellitus and varying levels of renal function. Diabetes Care 2010, 33: 1291–1293.
80. Jager J, Kooy A, Lehert P, Wulffelé M, et al: Long term treatment with metformin in patients with type 2 diabetes and risk of vitamin B-12 deficiency: randomized placebo controlled trial. BMJ 2010, 340: c2181.
81. Wei Ting RZ, Szeto CC, Chan M, Ma K, et al: Risk Factors of Vitamin B12 Deficiency in Patients Receiving Metformin. Arch Intern Med 2006, 166: 1975–1979.
82. Rojas and Gomes: Metformin: an old but still the best treatment for type 2 diabetes. Diabetology & Metabolic Syndrome 2013 5:6.
83. Glucophage W and Glucophage XRproduct information. Bristol-Myers Squibb Company. 2003. Available at: www.drugs.com/pro/glucophage.html.
84. Gershell L., Type 2 diabetes market, Nature Reviews | Drug Discovery, 2005, Vol 4, 367-368.

© 2017 Global Journals Inc. (US)