

CrossMark
click for updates

The impact of metformin in chronic kidney disease-mineral and bone disorder

Rohollah Masumi¹, Ramin Tolouian² , Audrey Tolouian³ , Leila Mohmoodnia¹ ¹Cancer Research Center, Shahrekord University of Medical Sciences, Shahrekord, Iran²Division of Nephrology, University of Arizona, Tucson, AZ, USA³School of Nursing, University of Texas, El Paso, TX, USA

ARTICLE INFO

Article Type:
Mini Review**Article History:**

Received: 2 April 2020

Accepted: 7 May 2020

Published online: 27 May 2020

Keywords:

Metformin, Chronic kidney disease-mineral and bone disorder (CKD-MBD), Bone fracture

ABSTRACT

Chronic kidney disease-mineral and bone disorder (CKD-MBD) is a disorder of mineral and bone metabolism due to chronic kidney disease (CKD). Bone disease and mortality are more common in patients with CKD. In addition of antidiabetic properties of metformin (MET), it possesses anti-inflammatory, anti-fibrotic properties and increases the markers of osteogenic effects. Therefore, it improves bone quality and decreases the risk of fractures in patients with type 2 diabetes. Metformin can also inhibit arterial calcification, maintain calcium-phosphorus balance, decrease cellular infiltration, fibrosis, and inflammation in kidney. Based on evidence, the prevalence of lactic acidosis due to metformin in patients with type 2 diabetes (T2D) and renal dysfunction is lower compared to other oral antidiabetic agents. Metformin decreases all-cause mortality in patients with diabetic nephropathy. The administration of metformin showed no difference in the prevalence of lactic acidosis in patients with T2D who had normal, mild, moderate, or severe renal dysfunction. Therefore, metformin can be used in patients with significant CKD to inhibit CKD-MBD due to its osteogenic effects.

Implication for health policy/practice/research/medical education:

Metformin can be used in patients with significant chronic kidney disease, while inhibiting CKD-MBD (chronic kidney disease-mineral and bone disorder) due to its osteogenic effects.

Please cite this paper as: Masumi R, Tolouian R, Tolouian A, Mohmoodnia L. The impact of metformin in chronic kidney disease-mineral and bone disorder. J Nephroarmacol. 2021;10(1):e02. DOI: 10.34172/npj.2021.02.

Calcium homeostasis and chronic kidney disease

Renal physiological functions can influence bone strength through the regulation of calcium excretion. More than 95% of filtered calcium is reabsorbed through the renal tubules and 60% of that reabsorption happens by diffusion transport. Calcium homeostasis is a very important process for human survival. Although calcium is a main element of the bony skeleton, it is also involved in many intra and extracellular pathways such as neuronal network, immune response, muscle contractions and hormone secretion. Total body calcium in an adult human is approximately 1-2 kg with 99% of it accumulates in the bone.

Less than 1% of total body calcium is in the extracellular space. Almost half of the extracellular calcium is in an ionized form, 40% protein-bound and 10% in a complex with anions such as phosphate, sulfate, citrate and so on. The ionized calcium is strongly regulated by parathyroid

hormone (PTH), 1,25-dihydroxyvitamin D₃, calcitonin and even calcium. All the mechanisms are regulating to keep the serum calcium concentration within a range of 8.5-10.5 mg/dL (1,2).

The kidney is the target organ of numerous regulatory hormones such as PTH and fibroblast growth factor-23 (FGF-23), and is the key organ to synthesize vitamin D. Chronic kidney disease is associated with bone fractures and significant reduction of bone mineral density as well as a significant increase in morbidity and mortality (3). The prevalence of MBD among patients on chronic hemodialysis is 85% based on abnormal PTH levels and around 64% based on symptoms (4).

It has been confirmed that decreased bone mineral density (BMD) is a powerful predictor of fracture risk in chronic kidney disease (CKD) patients. Identifying the causes of bone fracture such as hyperparathyroidism,

adynamic bone disease or biological aging osteoporosis is a difficult task based on bone densitometry results. In addition to bone disease related to the aging-kidney, renal diseases such as diabetic nephropathy can cause mineral bone diseases unrelated to aging. Therefore, CKD is a strong risk factor for augmented fracture (5).

Chronic kidney disease-mineral and bone disorder (CKD-MBD)

CKD-MBD is a disorder of mineral and bone metabolism caused by CKD that consists of either one or all of the following disorders: alteration of calcium, phosphorus, PTH or vitamin D metabolism, alteration of bone turnover, mineralization, volume, linear growth or strength, vascular or other soft-tissue calcification (5). CKD-MBD may lead to cardiovascular diseases, left ventricular hypertrophy, hypertension, immune dysfunction, inflammation and iron deficiency anemia (6).

It is estimated that 70%-90% of CKD patients in stages III-IV progress to developing abnormalities in bone and mineral homeostasis. Data from the National Health and Nutrition Examination Survey (NHANES) proposes that bone diseases are more prevalent in people with estimated glomerular filtration rates (eGFR) <60 mL/min/1.73 m² compared to those with eGFR >60 mL/min/1.73 m² (7).

Therefore, early diagnosis and therapeutic intervention may prevent bone and mineral disorders and change the outcomes (8-10).

A wide range of bone disorders has been identified in patients with chronic renal failure. Two main types of bone abnormalities observed in patients with end-stage renal disease (ESRD) are high-turnover and low-turnover osteodystrophy. High-turnover bone disease is characterized by the development of secondary hyperparathyroidism and eventually osteitis fibrosa. Low turnover or adynamic bone disease is characterized by a low number of osteoblasts with normal or reduced osteoclasts and osteomalacia. Over the past two decades, the incidence of high-turnover renal osteodystrophy has reduced as compared to low-turnover renal osteodystrophy.

The purpose of the treatment of renal bone disease is to reduce the prevalence of uremic bone disease in addition to decreasing cardiovascular morbidity and mortality caused by high levels of PTH in blood and calcium × phosphorus product (11,12).

Diabetes and bone diseases

It has been shown that patients with type 2 diabetes (T2D) have fewer bone formation markers, and less quality bone than non-diabetic individuals. Those differences are due to the role of hyperglycemia and toxic effects of advanced glycosylation end-products on bone tissue and reduced bone microvascular system (13). The patients with diabetes have higher risk of bone fracture, even in the presence of normal or high BMD or high body mass index

(14). Several factors may increase fractures in diabetic patients including; renal failure, antidiabetic drugs and higher incidence of falls (15). Osteoporosis is a common metabolic bone disease in patients with T2D. It has been shown that hyperglycemic conditions lead to adipogenic differentiation, impaired growth and enhanced apoptosis in osteoblasts instead of osteogenesis (16). Furthermore, it has been reported that control of glycemic status can contribute to normalizing high bone resorption in poorly controlled T2D (17). Therefore, appropriate control of glycemia in T2D patients is essential for bone health. The relationship between diabetes and bone diseases provides an opportunity for certain antidiabetic therapies, including Metformin, to affect bone function (18).

Metformin and bone metabolism

Metformin, a common antidiabetic drug, improves bone quality and decreases the risk of fractures in patients with T2D. The beneficial effects of metformin, especially its osteogenic effect, on bone metabolism have been confirmed (19). It has been shown that AMP-activated protein kinase (AMPK), as the main molecule in the antidiabetic mechanism of metformin, is effective in signaling pathways involved in bone physiology (20,21). Inflammation and fibrosis have direct effects on osteoporosis. Several inflammatory diseases such as arthritis, lupus, and cystic fibrosis are associated with bone resorption. Metformin has anti-inflammatory and anti-fibrotic properties and increases the markers of osteogenic differentiation (22). Moreover, metformin stimulates osteoprotegerin expression and differentiation in osteoblasts and suppresses bone loss in ovariectomized rats. It can reduce the receptor activation of nuclear factor-κB ligand and inhibit osteoclast differentiation in vitro (23). Metformin exerts the antidiabetic effects by stimulating AMPK via obstructing the mitochondrial respiratory chain and improving AMP/ATP ratio. The AMPK subunit α1 expresses in bone tissue, primary osteoblasts, and osteoclasts in addition to some bone cell lines (24). Thus, activation of AMPK by metformin can directly affect bone metabolism. Studies have also exhibited that metformin inhibits arterial calcification via the AMPK/ endothelial nitric oxide synthase (eNOS) pathway either directly or indirectly and can control vascular calcification. However, the exploration of other signaling mechanisms of metformin may contribute to the treatment of macrovascular disease and diabetes-related complications (11, 25). Metformin also stimulates osteoblast differentiation through inhibiting peroxisome proliferator-activated receptor-γ (PPARγ) (26). MET has direct osteogenic effects on bone via AMPK/Runx related transcription factor 2 (Runx2) and is indirectly effected by glycemic control (27,28). Recently, some studies have demonstrated that osteogenesis can be mediated by metformin (20,22,29). It has been shown that, glycogen synthase kinase 3 beta (GSK3β) and Wnt/β-catenin

signaling pathway is related to metformin -induced osteogenic differentiation of human bone marrow-derived mesenchymal stem cells (hBMSCs) (22). Kanazawa et al demonstrated that metformin induces the differentiation and mineralization of osteoblastic MC3T3-E1 via activating the AMPK signaling pathway and increasing expression of eNOS and bone morphogenetic protein-2 (30). In addition, Zhen et al investigated whether or not metformin can suppress the adverse effects simulated by hyperglycemia in primary osteoblast cell cultures. They found that treatment with metformin considerably reduced intracellular reactive oxidative species formation and osteoblast apoptosis, suggesting the beneficial effect of metformin is on the bone (31,32).

It is suggested that metformin stimulates adipose-derived human mesenchymal stem cells (Ad-hMSCs) in rats with osteoarthritis by increasing antinociceptive activity, anti-inflammatory and chondroprotective effects. Therefore, metformin can be a hopeful choice for the clinical application of Ad-hMSCs, as a cell therapy for osteoarthritis (33). Metformin can be beneficial in the protection of bone, particularly in the first stages of rheumatoid arthritis- reducing inflammation, cardiovascular disease and cancer. Therefore, metformin can be beneficial in enhancing quality of life for rheumatoid arthritis patients (34). Araújo et al showed that metformin decreases osteoporosis, inflammation and oxidative stress in ligature-induced periodontitis in rats (35).

Metformin, chronic kidney disease and lactic acidosis

Metformin can prevent the progression of severe CKD. Metformin protects renal tubular cells by blocking urinary crystal deposits and through its anti-oxidative effects (36). According to a recent study, metformin reduced hyperphosphatemia and hypocalcemia, inhibited vascular calcification, maintained calcium-phosphorus balance, decreased cellular infiltration, and fibrosis and inflammation in the kidneys of rats (11).

Metformin-associated lactic acidosis (MALA) is known as one of the adverse effects of metformin. However, MALA is rare in clinical cases of pre-existing CKD or progressive heart disease. Recently, there is strong evidence of metformin safety in patients with advanced stages of CKD, whereas previously, treatment with metformin was often withdrawn before iodinated contrast. It has been detected that, the prevalence of lactic acidosis under treatment with other oral anti-hyperglycemia (4.8 cases on 100 000 patient-years), is significantly higher than with metformin (3.3 cases on 100 000 patient-years) (37).

Metabolic acidosis may affect bone material directly by simulating dissolution of bone, bone resorption, preventing bone formation induced by osteoblast and changing the serum concentrations or activity of PTH and vitamin D. As a result, in some patients with normal renal function, osteoporosis and osteomalacia have been reported to be partly related to metabolic acidosis. In addition, the

severity of metabolic acidosis, before and after the start of dialysis, can affect the degree of hyperparathyroidism, osteodystrophia fibrosa and osteomalacia in patients with CKD (38).

Furthermore, no incidence or significant increases have been observed in lactate levels in the Cochrane analysis of 347 controlled trials with more than 70 490 patient-years (39). An analysis of more than 50 000 patients with T2D showed that metformin treatment is safe, even in patients with eGFR rate less than 30 ml/min/1.73 m² (40,41). A prospective cohort study in patients with diabetes and CKD stage 4 illustrated that treatment with low-dose metformin for one month is not associated with adverse effects, which supports safe administration of metformin in progressed stages of CKD (42). Moreover, a trial by Duong et al involved 22 patients with creatinine clearance of 15- 40 mL/min, and 2 patients undergoing dialysis with low daily doses of metformin (250–500 mg) displayed no symptoms of lactic acidosis (43).

Ekström et al indicated that the administration of metformin decreases the risk of all-cause mortality, acidosis, serious infection, or cardiovascular disease in patients with T2D and renal impairment (40). Based on a study by Richy et al, the administration of metformin showed no difference in the prevalence of lactic acidosis in patients with T2D who had normal, mild, moderate, or severe renal dysfunction (44). Recently, a retrospective observational cohort study by Lee et al, reported that metformin users probably develop ESRD and CKD more than non-metformin users (45). While Lalau et al reported no adverse effects for the use of metformin in different CKD stages (46).

Conclusion

Metformin, in addition to its antidiabetic properties, possesses anti-inflammatory and anti-fibrotic properties and increases the markers of osteogenic effects. Based on evidence, the administration of metformin does not cause lactic acidosis in T2D patients with renal dysfunction including CKD. Therefore, metformin can be used in patients with significant CKD and inhibit CKD-MBD due to its osteogenic effects. However, few studies have been conducted in this field and further trials are needed.

Authors' contribution

RM and LM searched the literature and prepared the manuscript. AT and RT edited the paper. All authors read and approved the final manuscript.

Conflicts of interest

The authors declared no competing interests.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

Funding/Support

The current study was not financially supported.

References

1. Jeon US. Kidney and calcium homeostasis. *Electrolyte Blood Press.* 2008; 6: 68–76. doi: 10.5049/EBP.2008.6.2.68
2. Hoenderop JG, Muller D, Van Der Kemp AW, Hartog A, Suzuki M, Ishibashi K, et al. Calcitriol controls the epithelial calcium channel in kidney. *J Am Soc Nephrol.* 2001;12:1342–9.
3. Nickolas TL, Leonard MB, Shane E. Chronic kidney disease and bone fracture: a growing concern. *Kidney Int.* 2008;74:721–31. doi: 10.1038/ki.2008.264.
4. Ahmed H, Elzorkany K, Yasein Y, et al. Prevalence of mineral bone disorders among hemodialysis patients in Menoufia Governorate, Egypt. *Menoufia Med J.* 2017;30: 687–92.
5. Bover J, Ureña-Torres P, Torregrosa JV, Rodríguez-García M, Castro-Alonso C, Górriz JL, et al. Osteoporosis, bone mineral density and CKD–MBD complex (I): Diagnostic considerations. *Nefrologia.* 2018;38:476–90. doi: 10.1016/j.nefro.2017.12.006.
6. Mosbah O. Chronic kidney disease-mineral and bone disorders (CKD-MBD). *Arch Nephrol Urol.* 2019;2:033–051. doi: 10.26502/anu.2644-2833008.
7. Khairallah P, Nickolas TL. Management of osteoporosis in CKD. *Clin J Am Soc Nephrol.* 2018;13(6):962–9. doi: 10.2215/CJN.11031017.
8. Miller PD. Chronic kidney disease and the skeleton. *Bone Res.* 2014;2:14044. doi: 10.1038/boneres.2014.44.
9. Sprague SM. Renal bone disease. *Curr Opin Endocrinol Diabetes Obes.* 2010;17:535–9. doi: 10.1097/MED.0b013e3283400945.
10. Bushinsky DA. Bone disease in moderate renal failure: Cause, nature, and prevention. *Annu Rev Med.* 1997;48:167–76. doi: 10.1146/annurev.med.48.1.167.
11. Neven E, Vervaet B, Brand K, Gottwald-Hostalek U, Opdebeeck B, De Maré A, Verhulst A, et al. Metformin prevents the development of severe chronic kidney disease and its associated mineral and bone disorder. *Kidney Int.* 2018;94:102–113. doi: 10.1016/j.kint.2018.01.027.
12. El-Kishawi AM, El-Nahas AM. Renal osteodystrophy: review of the disease and its treatment. *Saudi J Kidney Dis Transpl.* 2006;17:373–82.
13. Lecka-Czernik B. Diabetes, bone and glucose-lowering agents: basic biology. *Diabetologia.* 2017;60:1163–1169. doi: 10.1007/s00125-017-4269-4.
14. Vestergaard P. Discrepancies in bone mineral density and fracture risk in patients with type 1 and type 2 diabetes—a meta-analysis. *Osteoporos Int.* 2007;18:427–44. doi: 10.1007/s00198-006-0253-4.
15. Starup-Linde J, Eriksen SA, Lykkeboe S, Handberg A, Vestergaard P. Biochemical markers of bone turnover in diabetes patients—a meta-analysis, and a methodological study on the effects of glucose on bone markers. *Osteoporos Int.* 2014;25:1697–708. doi: 10.1007/s00198-014-2676-7.
16. Wang W, Zhang X, Zheng J, Yang J. High glucose stimulates adipogenic and inhibits osteogenic differentiation in MG-63 cells through cAMP/protein kinase A/extracellular signal-regulated kinase pathway. *Mol Cell Biochem.* 2010;338:115–22. doi: 10.1007/s11010-009-0344-6.
17. Okazaki R, Totsuka Y, Hamano K, Ajima M, Miura M, Hirota Y, Hata K, et al. Metabolic improvement of poorly controlled noninsulin-dependent diabetes mellitus decreases bone turnover. *J Clin Endocrinol Metab.* 1997;82:2915–20. doi: 10.1210/jcem.82.9.4258.
18. Vianna AGD, Sanches CP, Barreto FC. Review article: Effects of type 2 diabetes therapies on bone metabolism. *Diabetol Metab Syndr.* 2017;9:75–86. doi: 10.1186/s13098-017-0274-5.
19. Palermo A, D’Onofrio L, Eastell R, Schwartz AV, Pozzilli P, Napoli N. Oral anti-diabetic drugs and fracture risk, cut to the bone: safe or dangerous? A narrative review *Osteoporos Int.* 2015;26:2073–89. doi: 10.1007/s00198-015-3123-0.
20. Kanazawa I. Usefulness of metformin in diabetes-related bone disease. *Clin Calcium.* 2009;19:1319–25.
21. Schwartz AV. Diabetes, bone and glucose-lowering agents: clinical outcomes. *Diabetologia.* 2017;60:1170–9. doi: 10.1007/s00125-017-4283-6.
22. Ma J, Zhang ZL, Hu XT, Wang XT, Chen AM. Metformin promotes differentiation of human bone marrow derived mesenchymal stem cells into osteoblast via GSK3 inhibition. *Eur Rev Med Pharmacol Sci.* 2018;22:7962–8. doi: 10.26355/eurerv_201811_16424.
23. Mai QG, Zhang ZM, Xu S, Lu M, Zhou RP, Zhao L, et al. Metformin stimulates osteoprotegerin and reduces RANKL expression in osteoblasts and ovariectomized rats. *J Cell Biochem.* 2011;112:2902–9. doi: 10.1002/jcb.23206.
24. Shah M, Kola B, Bataveljic A, et al. AMP-activated protein kinase (AMPK) activation regulates in vitro bone formation and bone mass. *Bone.* 2010;47(2):309–19.
25. Zhang X, Xiao J, Li R, Qin X, Wang F, Mao Y, Liang W, et al. Metformin alleviates vascular calcification induced by vitamin D3 plus nicotine in rats via the AMPK pathway. *Vascul Pharmacol.* 2016;81:83–90. doi: 10.1016/j.vph.2016.01.002.
26. Gao Y, Xue J, Li X, Jia H, Hu J. Metformin regulates osteoblast and adipocyte differentiation of rat mesenchymal stem cells. *J Pharm Pharmacol.* 2008;60:1695–700. doi: 10.1211/jpp.60/12.0017.
27. Molinuevo MS, Schurman L, McCarthy AD, Cortizo AM, Tolosa MJ, Gangoiti MV, . Effect of metformin on bone marrow progenitor cell differentiation: in vivo and in vitro studies. *J Bone Miner Res.* 2010;25(2):211–21. doi: 10.1359/jbmr.090732.
28. Jiating L, Buyun J, Yinchang Z. Role of metformin on osteoblast differentiation in type 2 diabetes. *Biomed Res Int.* 2019;2019:9203934. doi: 10.1155/2019/9203934.
29. Smieszek A, Tomaszewski KA, Kornicka K, Marycz K. Metformin promotes osteogenic differentiation of adipose-derived stromal cells and exerts pro-osteogenic effect stimulating bone regeneration. *J Clin Med.* 2018;7:482. doi: 10.3390/jcm7120482.
30. Kanazawa I, Yamaguchi T, Yano S, Yamauchi M, Sugimoto T. Metformin enhances the differentiation and mineralization of osteoblastic MC3T3–E1 cells via AMP kinase activation as well as eNOS and BMP-2 expression. *Biochem Biophys Res Commun.* 2008;375:414–9. doi: 10.1016/j.bbrc.2008.08.034.
31. Zhen D, Chen Y, Tang X. Metformin reverses the deleterious effects of high glucose on osteoblast function. *J Diabetes Complications.* 2010;24:334–44.
32. Gilbert MP, Pratley RE. The impact of diabetes and diabetes medications on bone health. *Endocr Rev.* 2015;36:194–213.

- doi: 10.1210/er.2012-1042.
33. Park MJ, Moon SJ, Baek JA, Lee EJ, Jung KA, Kim EK, et al. Metformin augments anti-inflammatory and chondroprotective properties of mesenchymal stem cells in experimental osteoarthritis. *J Immunol.* 2019;203:127-36. doi: 10.4049/jimmunol.1800006.
 34. Son HJ, Lee J, Lee SY, Kim EK, Park MJ, Kim KW, Metformin attenuates experimental autoimmune arthritis through reciprocal regulation of Th17/Treg balance and osteoclastogenesis. *Mediators Inflamm.* 2014;2014:973986. doi: 10.1155/2014/973986.
 35. Araújo AA, Pereira ASBF, Medeiros CACX, Brito GAC, Leitão RFC, Araújo LS, et al. Effects of metformin on inflammation, oxidative stress, and bone loss in a rat model of periodontitis. *PLoS One.* 2017;12:e0183506. doi: 10.1371/journal.pone.0183506.
 36. Yang X, Ding H, Qin Z, Zhang C, Qi S, Zhang H, et al. Metformin prevents renal stone formation through an antioxidant mechanism in vitro and in vivo. *Oxid Med Cell Longev.* 2016;2016:4156075. doi: 10.1155/2016/4156075.
 37. Bodmer M, Meier C, Krähenbühl S, Jick SS, Meier CR. Bodmer M, Meier C, Krahenbuhl S, Jick SS, Meier CR. Metformin, sulfonylureas, or other antidiabetes drugs and the risk of lactic acidosis or hypoglycemia: a nested case-control analysis. *Diabetes Care.* 2008;31:2086-91. doi: 10.2337/dc08-1171.
 38. Kraut JA. The role of metabolic acidosis in the pathogenesis of renal osteodystrophy. *Adv Ren Replace Ther.* 1995;2:40-51. doi: 10.1016/s1073-4449(12)80070-7.
 39. Salpeter SR, Greyber E, Pasternak GA, Salpeter EE. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. *Cochrane Database Syst Rev.* 2010;(1):CD002967. doi: 10.1002/14651858.CD002967.
 40. Ekström N, Schioler L, Svensson AM, Eeg-Olofsson K, Miao Jonasson J, Zethelius B, et al. Effectiveness and safety of metformin in 51 675 patients with type 2 diabetes and different levels of renal function: a cohort study from the Swedish National Diabetes Register. *BMJ Open.* 2012;2:e001076. doi: 10.1136/bmjopen-2012-001076.
 41. Janić M, Volčanšek Š, Iunder M, Janež A. Metformin: from mechanisms of action to advanced clinical use. *Zdrav Vestn.* 2017;86:138-57. doi: 10.6016/ZdravVestn.1503.
 42. Dissanayake AM, Wheldon MC, Ahmed J, Hood CJ. Extending metformin use in diabetic kidney disease: a pharmacokinetic study in stage 4 diabetic nephropathy. *Kidney Int Rep.* 2017;2:705-712. doi: 10.1016/j.ekir.2017.03.005.
 43. Duong JK, Roberts DM, Furlong TJ, Kumar SS, Greenfield JR, Kirkpatrick CM, et al. Metformin therapy in patients with chronic kidney disease. *Diabetes Obes Metab.* 2012;14:963-5. doi: 10.1111/j.1463-1326.2012.01617.x.
 44. Richey FF, Sabido-Espin M, Guedes S, Corvino FA, Gottwald-Hostalek U. Incidence of lactic acidosis in patients with type 2 diabetes with and without renal impairment treated with metformin: a retrospective cohort study. *Diabetes Care.* 2014;37:2291-5. doi: 10.2337/dc14-0464.
 45. Lee MC, Lee CH, Chang LY, et al. Association of metformin use with end-stage renal disease in patients with type 2 diabetes mellitus: a nationwide cohort study under the pay-for-performance. *J Clin Pharmacol.* 2019;59:1443-52. doi: 10.1002/jcph.1452.
 46. Lalau JD, Kajbaf F, Bennis Y, Hurtel-Lemaire AS, Belpaire F, De Broe ME. Metformin treatment in patients with type 2 diabetes and chronic kidney disease stages 3A, 3B, or 4. *Diabetes Care.* 2018;41:547-553. doi: 10.2337/dc17-2231.

Copyright © 2021 The Author(s); Published by Society of Diabetic Nephropathy Prevention. This is an open-access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.