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Review Article

Metformin and Kidneys - A Contentious Relationship

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Abstract

Metformin has evolved as the most popular anti-diabetic medicine worldwide. Way back in 1998 United Kingdom *Prospective Diabetes Study (UKPDS) Group* had shown that it is the only oral hypoglycemic agent that has proven to reduce cardiovascular mortality in diabetes mellitus type 2 (DM2). Various reports have shown its safety but amongst many practitioners, there is still fear of lactic acidosis (LA). This concern is further heightened in diabetic patients with chronic kidney disease (CKD). Here we review if that is still a valid concern or not.

Keywords: Metformin; Chronic kidney disease; Lactic Acidosis

Introduction

Chemical and historical background

A French lilac called Galega officinalis had been used in past as a traditional medicine. A guanidine compound that could lower sugar in animal studies was found in its extract in 1920s [1]. Guanidine can be considered a nitrogenous analogue of carbonic acid. But it turned out to be too toxic for human use. Galegine (isoamylene guanidine) [2], another alkaloid extract from same plant and a different synthetic guanidine analog called Synthalin [3] were also studied for lowering blood sugar but were overshadowed by development and interest in insulin.

In late 1920s there was also development of a glucose lowering organic compound called Biguanide. One of those-Metformin (dimethylbiguanide), was found in 1920s but was then forgotten [4]. Then in 1957 a human trial was published with the name Glucophage (glucose eater) [5].In the next two years reports were published on phenformin [6] and buformin [7]. Later both phenformin and buformin were withdrawn from many countries due to their association with fatal lactic acidosis (LA). Due to similar reason, concerns developed for metformin but remarkably it remained available. It has been available in United Kingdom since 1958, but it finally became available in United States (US) in 1994.

Clinical use

Metformin is amongst those anti-diabetics that are recommended as first line therapy for diabetes mellitus type 2 (DM2) [8]. It is one of only two oral medicines in the World Health Organization essential medication list for DM2 [9]. Many studies in 1990s showed its effectiveness in countering insulin resistance without causing hypoglycemia, and in obese diabetics with lack of weight gain [10-12]. Along with lack of weight gain, it causes modest reduction in LDL and triglycerides [11]. It has been shown to reduce mortality through decreasing cardiovascular complications [13]. It is mostly not associated with risks of hypoglycemia unless there is excessive exercise, severe calorie reduction or mixed with other anti-diabetic medicine. Though it has been used in polycystic ovary syndrome [14], non-alcoholic fatty liver disease [15], and for premature puberty [16], its major use remains in control of DM2.

Risks of Lactic Acidosis

LA remains the most feared risk associated with biguanides mostly with phenformin. It is the L-Lactate that accumulates in case on biguanides. Because mortality rates of 30% to 50% were described in literature in early 1990s, phenformin was removed from the market [11]. Though chemically similar, metformin has different mechanism of action. Still however, because of fear of LA, metformin had many contraindications attached to it.

Although circumstantial evidence supports that metformin use may be linked with LA- termed metformin associated lactic acidosis (MALA), no definitive causal relationship has been proven. It has a short half-life and is renally excreted solely. By itself, metformin has not been shown to be responsible to affect the concentration of lactate in DM2. Many reported cases of MALA did not measure metformin levels and in those that were measured, many did not have high levels - hence many of those could be "metformin coincident lactic acidosis" [17]. Rates of LA in USA that were reported before the approval of metformin were no different from the rates found in those using metformin [18]. Further suggesting that metformin could not be fully implicated in all those cases reported as MALA.

The reports in literature about patients with MALA include patients with many risk factors and so difficult to interpret the literature [19]. DM is in itself risk factor for lactic acidosis and so many reported cases may just have been lactic acidosis due to just DM itself. Various putative risk factors for LA with metformin has been described in literature, including old age, decreased cardiac or hepatic function or chronic kidney disease (CKD), diabetic ketoacidosis, respiratory failure, ethanol intoxication, fasting and hypoxic conditions [19]. In a nested case-control analysis, out of 50,048 patients, 6 patients were identified with active use of metformin and MALA. 5 of those suffered from sepsis and acute organ dysfunction, suggesting as others have shown that MALA mostly occurs in acutely worsening clinical conditions [20].

The review of literature does not support the notion that the incidence of MALA is so rare because guidelines for contraindications are followed. Many have reported its use in those with risks, without any significant complications. In one report of 47 patients who developed LA on metformin, 43 had one or more risk factors for lactic

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acidosis including congestive heart failure and renal insufficiency [18]. A Medline search for English language articles published between January 1966 to May 2008 about studies on metformin and heart failure was conducted. Though conducted epidemiological data show that despite frequent use of metformin in congestive heart failure (CHF), there were no new MALA case reports noted [21]. The US Food and Drug Administration (FDA) have removed heart failure as a contraindication for metformin use in 2006, since reduction in all-cause mortality with metformin use was demonstrated in diabetics with heart failure [22]. Several studies have shown that metformin does not raise lactate levels even in elderly and in those with reduced renal function [23]. In another report of 308 patients with DM2, even though 73% patients had contraindication or risk factors, none developed LA [24].

Review of cases of LA published between May 1995 and January 2000, concluded that no mortality was associated with metformin alone [25]. In a review of 398 metformin overdoses with a median intake of 15 g, only 14 (3.5%) patients developed LA [26]. In a review of 49 metformin treated patients who had also developed LA, higher metformin levels did not consistently occurred in cases with more severe LA and did not correlate with higher mortality [27]. A review of literature done by Terpening showed that vast majority of case series have failed to establish any correlation between metformin levels and either lactate or pH. Also those with higher metformin levels had better survival in cases of MALA compared to those who did not survive [17]. In another review of cases of LA, 10 patients were diagnosed with MALA out of 197. All 10 had toxic metformin levels and median serum Cr of 796μmol/l (9.0 g/dl). Though all MALA patients had pH <7.0, only 31/187 patients with general LA had pH <7. There was 50% survival in MALA versus 0% in general LA group if arterial blood pH <7.00. Overall the mortality of up to 83% was reported with LA in general compared to 30-50% mortality with MALA [28]. In fact, it has been hypothesized that there may be some protective effects of metformin in MALA [17], and also it may even be protective in shock [27].

However it has also been shown that the in comparison, the incidence of hypoglycemia from oral sulfonylureas like glibenclamide was significantly greater than that of MALA. Same review showed that mortality risks for both sulfonylurea induced hypoglycemia and MALA were same [29].

Finally Salpeter et al. finally conducted a Cochran review in 2010. They reviewed 347 prospective trials and cohort studies with more than 70,490 patient-years of metformin use. 97% of these studies had at least one contraindication. They concluded that metformin was not associated with increased risk of LAs compared with other anti-diabetic medicines. Overall the risks appear to be mostly from co-morbidities that result in tissue hypoxia [30].

Rates and Incidence

A baseline rate of LA of 9.7 per 100,000 patient years was reported in USA when no biguanides were available in USA- similar to general population rates [31]. When phenformin was still available and prescribed, the original reports of LA rates were about 40-129 per 100,000 patient years [23,32,33]. However for metformin the reported rates have been as low 0-8.4 cases per 100,000 person years [12]. Package insert from manufacturer reports a rate of 3 per 100,000 patient years [34]. In Canada till 1998, there were no reported cases of metformin associated lactic acidosis when used as indicated [35]. Of the 28 reported cases all had some contraindication. In the first known population based longitudinal (16 year) study, the rate of LA in Canada was 9 per 100,000 person-years [33]. A rate of 3.3 cases per 100,000 person-years was reported from United Kingdom, amongst metformin users and 4.8 cases per 100,000 person-years amongst sulfonylurea users [20]. A much higher rate of 47 per 100,000 patient-years was reported from a group in Netherlands. They identified 16 cases of MALA. 9 of those had normal metformin levels but all had comorbidities that could confound the results [36]. In 2010 Cochrane review found that based on statistical inference, the incidence for lactic acidosis was 4.3 cases per 1000,000 patient-years, compared to 5.4 cases per 1000,000 patient-years in non-metformin group [30].

Kidney and Metformin

Renal failure is often cited as a contraindication to Metformin and it remains most important contraindication as few cases of LA without renal dysfunction have been described [37]. Current US Food and Drug Administration prescribing guidelines contradict Metformin's use in men with serum creatinine (Cr) of > 1.5 mg/dl and in women with serum Cr > 1.4 mg/dl. With the more common use of glomerular filtration rate (GFR), there may be an apparent abnormality in one and not the other measurement of renal function. These guidelines are arbitrary and may be outdated. The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI) notes that metformin should not be given beyond these levels of Cr. However their reference is from an article published in 1997 by Davidson et al. [38]. The limitations of serum Cr predicting GFR are well known know. This adds to the confusion for a physician.

Renal failure can cause metformin to accumulate, but in most cases tissue hypoxemia is a major inciting factor and it is the tissue hypoxia that seems to influence mortality and not the accumulated metformin levels [39]. Lalau et al. have shown that even if 850mg/day of metformin was given to elderly patients with creatinine clearance (CrCl) of 30-60 ml/min or 1700 mg/day if CrCL >60 ml/min, then there was no significant difference in measured serum levels of metformin and lactate between two groups [40]. A study was conducted in 24 patients with CrCl of 15-49 ml/min. No correlation was found between plasma lactate and metformin concentrations and authors suggested safety of its use with lower dosages at GFRs as low as 20ml/min. Two of their patients were even on dialysis also [41]. In a set of 59 diabetic patients on metformin, with age 73.9 + 10.3 years and CrCl of 38.5 + 13.4 ml/min, there was no incidence of LA reported [24].

Another study measured GFR based on cystatin C levels. Median dose of metformin was 1500 mg. Median metformin serum level was 4.5μmol/L (range 0.1-20.7) in GFR >60 ml/min/1.73 m^2, and 8.9μmol/l (range 6-18.6) with GFR <30 ml/min/1.73m^2. At usual doses, the steady-state plasma concentrations are generally <7.8μmol/l. This study showed that even at lower GFR levels rarely would metformin levels go above 20μmol/l, and this may be a safe level, though in actuality, exact unsafe metformin level is not known. It is still not known if measurement of these levels predicts MALA, since there is no correlation or any known relationship between renal function, metformin levels and MALA [42].

In the Fremantle diabetes study the risk of lactic acidosis was no different with metformin compared to other blood glucose-lowering therapies, even though about a third of patients on metformin had contraindications including renal and heart failure [43]. Another study from Scotland showed that there was only one case of lactic acidosis out of 4600 patient-years and 24.5% of those patients had a contraindication to metformin use including renal failure and cardiac failure [44]. In a study from Thailand, out of 1630 patients on metformin, 315 patients had at least one contraindication to metformin. Of those 315 patients, 203 had renal failure, but none developed lactic acidosis over 4 years [45]. In another study of 393 patients with serum Cr ranging from 1.5 to 2.5 mg/dl, were divided into those who continued and those who did not continue metformin. After 4 years no cases of lactic acidosis were found in either group, suggesting that avoiding metformin at such higher Cr levels did not alter risk of lactic acidosis [46]. Population studies in USA have shown that use of metformin in mild to moderate CKD is not very unusual. In one case, amongst those treated with metformin, 4.5 % had Cr greater than predefined safety limits [47]. In another analysis from University of Chicago diabetes center, 15.3% patients with GFR of <60ml ml/min/1.73m^2 were receiving metformin [48].

Investigators with the Reduction of Atherothrombosis for Continued Health (REACH) did a large observational study of > 19,000 subjects with history of atherothrombotic disease, 1,572 patients were using metformin with GFR 30-60 ml/min/1.73m^2. After adjustment for baseline factors and propensity score, metformin was associated with significant reduction in 2-year mortality including those with CKD They found that metformin was associated with 24% reduction in all-cause mortality. In moderate renal impairment (creatinine clearance 30-59 ml/min/1.73m^2); there was 36% reduction [49].

A cohort study from Swedish National Diabetes Register reviewed 51675 patients with DM2 and a mean follow up of 3.9 years. Metformin, compared with any other treatment, showed 13% reduction in all-cause mortality, and reduced risks of acidosis/serious infection in those with GFR of 45-60 ml/min/1.73m^2. With GFR of 30 to 45 ml/min/1.73m^2, similar benefit was not observed but neither was any increased risk of acidosis/serious infection was noted [50].

In the Cochran Analysis, although individual Cr levels were not available, 45% of studies reviewed did not exclude patients with a Cr >1.5 mg/dl. This equated to 37.360 patient-years of metformin use in studies including CKD patients that did not lead to any LA [30].

Despite the current U.S. prescribing guidelines, there is enough evidence of safety with its use in GFR as low as 30 ml/min/1.73m^2. Hence many nations have already adopted this as a recommendation [51]. In Australia, recently published National Evidence Based Guidelines for blood glucose control in DM2 have suggested that metformin though still contraindicated if GFR <30 ml/min/1.73m^2, can still be used with caution in those with GFR of 30-45 ml/min/1.73m^2 [52]. Canadians have similar guidelines [53]. The joint Position Statement of the American Diabetes Association and European Association for the Study of Diabetes agrees with this mention that it is reasonable to use of metformin down to GFR of 30 ml/min/1.73m^2, with dose reduction at GFR of 45 ml/min/1.73m^2 [54]. However frequent check of GFR is always recommended in such cases [55]. Even the cutoff of 30ml/min/1.73m^2 GFR is arbitrary and Mani has reported use in more than 1000 patients with CKD sages 3 and 4 and never seen a case of LA due to metformin [56].

Conclusion

Current guidelines on stopping metformin are vague. Because of its cost as well as benefits more wide use of metformin is needed, without the fear of concomitant LA. In poor countries use of cheap medicines like metformin may be the only option for DM2 management. A simplified and pragmatic set of guidelines is needed emphasizing the importance of renal clearance as well as importance of its withdrawal in the presence of or when there is impending tissue hypoxia [30].

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References

1. Bailey CJ, Day C. Metformin: its botanical background. PractDiab Int. 2004; 21: 115-117.
2. Muller H, Rheinwein H. Pharmacology of galegin. Arch Exp Path Pharmacol.1927; 125: 212–228.
3. Frank E, Nothmann M, Wagner A. Uber synthetischdargestellteKor permit insulin artiger Wirkung auf den normalen und den diabetischen Organismus. KlinWschr. 1926; 5: 2100–2107.
4. Werner E, Bell J. The preparation of methylguanidine, and of ßß-dimethylguanidine by the interaction of dicyanodiamide, and methylammonium and dimethylammonium chlorides respectively. J ChemSoc Transactions. 1921; 121:1790–1795.
5. Sterne J. Du nouveau dans les antidiabetiques. La NN dimethylamineguanylguanide (N.N.D.G.). Maroc Med.1957; 36:1295–1296.
6. Ungar G, Freedman L, Shapiro SL. Pharmacological studies of a new oral hypoglycemic drug. Proc Soc Exp Biol Med. 1957; 95: 190-192.
7. MehnerT H, Seitz W. [Further results of diabetes therapy with blood sugar lowering biguanides]. Munch Med Wochenschr. 1958; 100: 1849-1851.
8. IDF Clinical Guidelines Task Force. Global Guideline for Type 2 Diabetes: recommendations for standard, comprehensive, and minimal care. Diabet Med. 2006; 23: 579-593.
9. World Health Organization. WHO model list of Essential Medicines. 2013.
10. Campbell IW, Howlett HC. Worldwide experience of metformin as an effective glucose-lowering agent: a meta-analysis. Diabetes Metab Rev. 1995; 11 Suppl 1: S57-62.
11. Bailey CJ. Biguanides and NIDDM. Diabetes Care. 1992; 15: 755-772.
12. Bailey CJ, Turner RC. Metformin. N Engl J Med. 1996; 334: 574-579.
13. [No authors listed]. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998; 352: 854-865.
14. Mathur R, Alexander CJ, Yano J, Trivax B, Azziz R. Use of metformin in polycystic ovary syndrome. Am J Obstet Gynecol. 2008; 199: 596-609.
15. Haukeland JW, Konopski Z, Eggesbø HB, von Volkmann HL, Raschpichler G, Bjøro K, et al. Metformin in patients with non-alcoholic fatty liver disease: a randomized, controlled trial. Scand J Gastroenterol. 2009; 44: 853-860.
16. Ibáñez L, López-Bermejo A, Díaz M, Marcos MV, de Zegher F. Early metformin therapy (age 8-12 years) in girls with precocious pubarche to reduce hirsutism, androgen excess, and oligomenorrhea in adolescence. J Clin Endocrinol Metab. 2011; 96: E1262-1267.
17. Terpening C. MALAdaptive: do we avoid metformin unnecessarily? J Am Board Fam Med. 2014; 27: 136-141.

18. Misbin RI, Green L, Stadel BV, Gueriguian JL, Gubbi A, Fleming GA, et al. Lactic acidosis in patients with diabetes treated with metformin. N Engl J Med. 1998; 338: 265-266.

19. Luft FC. Lactic acidosis update for critical care clinicians. J Am Soc Nephrol. 2001; 12 Suppl 17: S15-19.

20. Bodmer M, Meier C, Krähenbühl S, Jick SS, Meier CR. Metformin, sulfonylureas, or other antidiabeties drugs and the risk of lactic acidosis or hypoglycemia. Diabetes Care. 2008; 31: 2086-2091.

21. Swift TMM. Metformin use in patients with diabetes and heart failure: cause for concern? Diabetes Spectrum. 2009; 22:18-20.

22. Tahrani AA, Varughese GI, Scarpello JH, Hanna FW. Metformin, heart failure, and lactic acidosis: is metformin absolutely contraindicated? BMJ. 2007; 335: 508-512.

23. Heaf JG, Biesen EV. Metformin and chronic renal impairment: A story of choices and ugly ducklings. Clin Diabetes. 2011; 29: 97-101.

24. Holstein A, Nahrwold D, Hinze S, Egberts EH. Contra-indications to metformin therapy are largely disregarded. Diabet Med. 1999; 16: 692-696.

25. Lalau JD, Race JM. Lactic acidosis in metformin therapy: searching for a link with metformin in reports of 'metformin-associated lactic acidosis'. Diabetes Obes Metab. 2001; 3: 195-201.

26. Wills BK, Bryant SM, Buckley P, Seo B. Can acute overdose of metformin lead to lactic acidosis? Am J Emerg Med. 2010; 28: 857-861.

27. Lalau JD, Race JM. Lactic acidosis in metformin-treated patients. Prognostic value of arterial lactate levels and plasma metformin concentrations. Drug Saf. 1999; 20: 377-384.

28. Friesecke S, Abel P, Roser M, Felix SB, Runge S. Outcome of severe lactic acidosis associated with metformin accumulation. Crit Care. 2010; 14: R226.

29. Campbell IW. Metformin and glibenclamide: comparative risks. Br Med J (Clin Res Ed). 1984; 289: 289.

30. Salpeter SR, Greyber E, Pasternak GA, Salpeter EE. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus (Review). Cochran Database Syst Rev. 2010; 4: CD002967.

31. Brown JB, Pedula K, Barzilay J, Herson MK, Latare P. Lactic acidosis rates in type 2 diabetes. Diabetes Care. 1998; 21: 1659-1663.

32. Aguilar C, Reza A, García JE, Rull JA. Biguanide related lactic acidosis: incidence and risk factors. Arch Med Res. 1992; 23: 19-24.

33. Stang M, Wysowski DK, Butler-Jones D. Incidence of lactic acidosis in metformin users. Diabetes Care. 1999; 22: 925-927.

34. Metformin package insert. Princeton, NJ; Bristol-Myers Squibb; 2008.

35. Copendium of Pharmaceuticals and Specialties, 33 edn. Ottawa: Canadian Pharmacists Association 1998; 673.

36. van Berlo-van de Laar IR, Vermeij CG, Doorenbos CJ. Metformin associated lactic acidosis: incidence and clinical correlation with metformin serum concentration measurements. J Clin Pharm Ther. 2011; 36: 376-382.

37. Ellis AK, Iliescu EA. Metformin-associated lactic acidosis in a low risk patient. Can J Clin Pharmacol. 2001; 8: 104-106.

38. Davidson MB, Peters AL. An overview of metformin in the treatment of type 2 diabetes mellitus. Am J Med. 1997; 102: 99-110.

39. Lalau JD, Lacroix C, De Cagny B, Fournier A. Metformin-associated lactic acidosis in diabetic patients with acute renal failure. A critical analysis of its pathogenesis and prognosis. Nephrol Dial Transplant. 1994; 9 Suppl 4: 126-129.

40. Lalau JD, Vermersch A, Hary L, Andrejak M, Isnard F, Quichaud J, et al. Type 2 diabetes in the elderly: an assessment of metformin (metformin in the elderly). Int J Clin Pharmacol Ther Toxicol. 1990; 28: 329-332.

41. 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: 963-965.

42. Frid A, Sterner GN, Löndahl M, Wiklander C, Cato A, Vinge E, et al. Novel assay of Metformin levels in patients with type 2 diabetes and varying levels of renal function: clinical recommendations. Diabetes Care. 2010; 33:1291-1293.

43. Kamber N, Davis WA, Bruce DG, Davis TM. Metformin and lactic acidosis in an Australian community setting: the Fremantle Diabetes Study. Med J Aust. 2008; 188: 446-449.

44. Emslie-Smith AM, Boyle DIR, Evans JMM, Sullivan F, Morrist AD: DARTS/MEMO Collaboration. Contraindications to metformin therapy in patients with type 2 diabetes---a population-based study of adherence to prescribing guidelines. Diabet Med. 2001; 18:483-488.

45. Pongwecharak J, Tengmeesri N, Malanusorn N, Panthong M, Pawangkapin N. Prescribing metformin in type 2 diabetes with a contraindication: prevalence and outcome. Pharm World Sci. 2009; 31: 481-486.

46. Rachmani R, Slavachevski I, Levi Z, Zadok B, Kedar Y, Ravid M, et al. Metformin in patients with type 2 diabetes mellitus: reconsideration of traditional contraindications. Eur J Intern Med. 2002; 13: 428.

47. Kennedy L, Herman WH; GOAL A1C Study Team. Renal status among patients using metformin in a primary care setting. Diabetes Care. 2005; 28: 922-924.

48. Vasisht KP, Chen SC, Peng Y, Bakris GL. Limitations of metformin use in patients with kidney disease: are they warranted? Diabetes Obes Metab. 2010; 12: 1079-1083.

49. Roussel R, Travert F, Pasquet B, Wilson PW, Smith SC Jr, Goto S, et al. Metformin use and mortality among patients with diabetes and atherothrombosis. Arch Intern Med. 2010; 170: 1892-1899.

50. Ekström N, Schiöler 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.

51. National Institute for Health and Clinical Excellence. The management of Type 2 diabetes: 2010 NICE guidelines. London, UK, National Institute for Health and Clinical Excellence. 2009.

52. Colagiuri S, Dickinson S, Girgis S, Colagiuri R. National Evidence Based Guideline for Blood Glucose Control in Type 2 Diabetes. Diabetes Australia and the NHMRC. Canberra 2009.

53. Canadian Diabetic Association. Clinical practice guideline. 2013.

54. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E. 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; 35:1364-79.

55. Lipska KJ, Bailey CJ, Inzucchi SE. Use of metformin in the setting of mild-to-moderate renal insufficiency. Diabetes Care. 2011; 34: 1431-1437.

56. Mani MK. Metformin in renal failure--weigh the evidence. Nephrol Dial Transplant. 2009; 24: 2287-2288.

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