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Use of Metformin in Diseases of Aging

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Abstract

Metformin is the most commonly prescribed medication for type 2 diabetes (T2DM) in the world. It has primacy in the treatment of this disease because of its safety record and also because of evidence for reduction in the risk of cardiovascular events. Evidence has accumulated indicating that metformin is safe in people with stage 3 chronic kidney disease (CKD-3). It is estimated that roughly one-quarter of people with CKD-3 and T2DM in the United States (well over 1 million) are ineligible for metformin treatment because of elevated serum creatinine levels. This could be overcome if a scheme, perhaps based on pharmacokinetic studies, could be developed to prescribe reduced doses of metformin in these individuals. There is also substantial evidence from epidemiological studies to indicate that metformin may not only be safe, but may actually benefit people with heart failure (HF). Prospective, randomized trials of the use of metformin in HF are needed to investigate this possibility.

Keywords

type 2 diabetes; chronic kidney disease; heart failure; lactic acidosis; pharmacotherapy; metformin; diseases; aging

Introduction

Cardiovascular (CV) disease is the leading cause of death in the US. Individuals with type 2 diabetes (T2DM), have a 2- to 4-fold increase in CV risk over and above that explained by conventional risk factors (1). It has been estimated that up to 75% of people with T2DM will die of a CV event (2). The remarkable linkage between T2DM and CV disease is not fully understood, but insulin resistance likely plays a prominent role (3). Insulin resistance, T2DM and CV diseases increase sharply with age (4; 5).

Over the past 2 decades, metformin, a biguanide, has emerged as first line treatment of T2DM. With a molecular weight of 129, metformin is the smallest of numerous small molecules (sulfonylureas, thiazolidinediones, α -glucosidase inhibitors, etc.) available for the

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Conflict of Interest

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treatment of this disease. Synthesis of metformin was first reported in the same year (6) as the landmark paper of Banting and Best describing the discovery of insulin (7). Appreciation of its value in diabetes treatment came later, and it is now the most widely prescribed antidiabetic drug in the world; a joint declaration of the American Diabetes Association and the European Association for the Study of Diabetes in 2006 endorsed this consensus (8). The chief reason for this is a favorable effect on risk of CV events (9), as shown in the United Kingdom Prospective Diabetes Study (UKPDS) (10). In the metformin arm of that study, obese individuals with newly diagnosed T2DM were randomized to metformin or diet alone and followed for a median of 11 years. Metformin reduced myocardial infarction by 39% compared to diet alone. The reduction in CV events is durable; in a 20 year follow-up report, there was a persistent 33% reduction in myocardial infarction in spite of a convergence in HbA1c early in the follow-up period, a “legacy effect” (11). In a recent analysis of >20,000 people with T2DM with atherosclerosis in the REACH registry, metformin use was associated with 24% lower all-cause mortality (12).

The mechanism for metformin’s favorable effects on CV events in T2DM is poorly understood. Review articles tend to emphasize the systemic effects of metformin after it is absorbed from the gastrointestinal (GI) tract (13; 14), chiefly acute glucose-lowering due to inhibition of gluconeogenesis (15). However, there is an additional effect of potential importance, one that is not systemic but rather may be exerted in the intestinal lumen, considering that 50% of the metformin dose is not absorbed (16). Some investigators have suggested that metformin causes bile acid malabsorption (17), an effect that could alter gastrointestinal motility and potentially influence satiation. An effect on motility could explain the blunting of the postprandial increase in plasma glucose (and also in the postprandial insulin response) that has been reported with metformin therapy (18). Metformin consistently produces a modest, but significant weight loss of 2–3 kg within 4–6 months of initiating therapy (19; 20). This effect appears to be due to a 250–300 kcal decrease in daily food intake (21). Although individuals who take metformin long term are not immune to weight gain, their weight remains significantly lower than people who are treated with sulfonylureas and insulin (10). Weight loss of modest degree has an underrated effect on glycemic control in T2DM. In fact, marked improvement in glycemic control occurs within 3 days of starting a low calorie diet (22) due to an improvement in insulin sensitivity that precedes weight loss (23). Whether metformin’s effect on weight, mediated by a decrease in energy intake, is responsible for beneficial effects on CV outcomes is not known. It is noteworthy, however, that in a prospective analysis of ~5000 individuals with T2DM, *intentional* weight loss of a modest degree was associated with a 28% decrease in CV mortality (24). The effect of metformin on gastrointestinal motility is largely unexplored.

Metformin is widely considered to be an insulin sensitizer. Individuals participating in the BARI-2D study were randomized to receive insulin provision therapy or insulin sensitization therapy, and metformin was considered to be in the latter category (25). In a literature search we found 97 articles that referred to metformin as an insulin sensitizer (42 of them from 2010–2013); 40 of these were published in endocrinology or diabetes journals (unpublished observations). However, it has been pointed out that the magnitude of improvement in insulin sensitivity produced by metformin treatment is similar to the

improvement observed when glycemic control is improved by sulfonylureas or insulin (26). Metformin (unlike thiazolidinediones) does not appear to have effects on adipose tissue lipolysis and free fatty acid availability, an important mediator of insulin sensitivity (27). Some investigators have suggested that improvement in insulin sensitivity during metformin therapy is dependent on weight loss (28). Whether or not metformin is an insulin sensitizer, it achieves glycemic control via a mechanism that is different from insulin and sulfonylureas. These latter agents improve glycemia by exogenous and endogenous insulin provision, respectively, and tend to promote weight gain. Metformin, on the other hand, improves glycemia while lowering insulin concentrations. It has the dual effect of reducing hepatic gluconeogenesis and promoting modest weight loss. Metformin's effect on insulin sensitivity may thus be partially indirect, but no less salutary.

Chronic Kidney Disease

The kidney plays a prominent role in metformin pharmacokinetics. Absorption of an oral dose of metformin is complete after ~6 hours, but a significant fraction of the dose is malabsorbed (16). The acute half-life ($t_{1/2}$) of metformin in blood is 2–6 hours after an oral dose (16), but with chronic therapy the $t_{1/2}$ is 8–20 hours because of a large intracellular pool of drug (29). Using an LC/MS/MS-based method for measuring plasma metformin, we have recently performed preliminary studies on metformin pharmacokinetics in people with T2DM. As can be seen in Figure 1, plasma metformin concentrations increase progressively after an oral dose of the immediate release preparation for at least 4 hours. Intestinal absorption is facilitated by organic cation transporters (OCT), which also mediate hepatic and renal uptake (30). Intestinal absorption is saturable (30); therefore, fractional malabsorption of the drug is greater at higher doses and reduced at lower doses (16). Metformin is excreted unchanged by the kidney, and its clearance is dependent on glomerular filtration rate (GFR) (31). In addition to excretion via filtration, there is active tubular secretion of metformin (31).

Chronic kidney disease (CKD) is a common condition that increases dramatically with age. There is a universal or near-universal decline in GFR with aging (32; 33); the lifetime risk of stage 3 CKD (CKD-3, with GFR 30–59 ml/min/1.73 m²) is ~60%, with onset occurring after age 70 in one-half of patients (34). Recent NHANES data indicates that the prevalence of CKD-3 increases by more than an order of magnitude after age 59 (35). It should be emphasized that physiological senescence of the kidney occurs with even healthy aging (36). In a study of 1344 potential kidney donors, cortical volume declined with age in both men and women with an accelerated rate of decline after age 50 years (37). A study of 1203 actual kidney donors found the prevalence of nephrosclerosis (glomerulosclerosis, tubular atrophy, interstitial fibrosis, and arteriosclerosis) on renal biopsy to increase linearly from 2.7% in 18–29 year olds to 73% in 70 to 77 year olds (32).

CKD is associated with high cardiovascular risk (38) and is a common complication of diabetes. Data from the National Health and Nutrition Examination Survey (NHANES) indicates that the prevalence of CKD-3 is ~20% in people with T2DM (39–41). Unfortunately, abnormal renal function (defined as a serum creatinine >1.4 mg/dL in men and > 1.3 mg/dL in women) is a contraindication to the use of metformin (see package insert

link, next page), reflecting a widespread perception that metformin cannot be used safely unless renal function is normal (42). Roughly one-quarter of people with CKD-3 in the NHANES survey have serum creatinine levels above the allowable range for metformin use (C. Koro, personal communication); considering that roughly 23 million Americans have T2DM, it can be estimated that well over 1 million people with CKD-3 and T2DM are ineligible for metformin treatment on the basis of their serum creatinine. A review of metformin use in the United Kingdom suggested that metformin use would be appropriate with serum creatinine values <1.8 mg/dL in both men and women (43).

Unfortunately, these studies are based on data obtained prior to serum creatinine standardization (44). Furthermore, it is GFR, not serum creatinine, which determines renal clearance of metformin. A standardized serum creatinine threshold of 1.4 in men and 1.3 in women can represent an estimated GFR (eGFR) anywhere from 39 to 77 mL/min/1.73m², depending on the patients age and race. Likewise, a serum creatinine threshold of 1.8 represent an eGFR of 26 to 57 mL/min/1.73m² (see http://www.kidney.org/professionals/kdoqi/gfr_calculator.cfm). The inaccuracy of serum creatinine in estimating GFR is reflected in the wide range of serum creatinine values for CKD-3 in different age, sex and race groups (Table 1). Estimated GFR is reported in units of mL/min/1.73 m², as this is optimal for CKD staging and classification (i.e., larger individuals require a greater GFR than smaller individuals). But GFR in units of mL/min is more relevant for drug clearance (calculated by multiplying by body surface area / 1.73 m²). Given the variation of body surface area in the population, the range of serum creatinine values that can represent a GFR of 30 to 59 mL/min is even wider than what is shown in Table 1.

Lingering concerns about the risk of lactic acidosis still limit the use of metformin in the hands of some practitioners. These concerns have their origins in the experience with phenformin, which is associated with a frequency of lactic acidosis of 1 in 1000 people who take it (45). The experience with phenformin may account in part for the nearly 50 year interval between metformin's approval for use in the United Kingdom (1958) and in the United States (1995). However, there is substantial epidemiological evidence that metformin therapy is safe and may actually be beneficial in people with decreased GFR. One study of >50,000 individuals with T2DM in the Swedish Diabetes Registry (46) suggested that metformin is well tolerated in people with eGFR values as low as 30 mL/min/1.73m². A review of metformin use in NHANES revealed that 20–40% of T2DM individuals with eGFR values of 30–59 mL/min/1.73m², including those with creatinine levels >1.5 mg/dL were taking metformin, with no increase in the frequency of lactic acidosis (47). The apparent safety of metformin use in these populations is particularly noteworthy considering that there are no established guidelines for using lower metformin doses in people with reduced GFR, and therefore, presumably, many individuals with low GFR but normal serum creatinine levels are given a “full” dose of at least 1700–2000 mg/day.

The creatinine thresholds for use of metformin are based on concerns about drug retention and resulting increased risk of lactic acidosis, the only potential serious risk of metformin treatment. The majority of prospective, randomized studies have found an increase in blood lactate concentrations in people taking metformin (48–50). However, the effect is relatively modest (a 20–50% increase), with mean lactate concentrations consistently <2.0 mmol/L

(49; 50). Most evidence indicates that metformin confers little if any risk of lactic acidosis. A recent large (>100,000 patient-years) meta-analysis found the upper limit for the incidence of lactic acidosis to be 4.3 and 5.4 cases per 100,000 patient-years in metformin treated and untreated T2DM patients, respectively (51). Moreover, when lactic acidosis does occur in patients taking metformin, it tends to be of the type A (hypoxemic) rather than type B (non-hypoxemic) variety (52), suggesting that metformin is not the cause of the lactic acidosis in these individuals. In spite of this reassuring evidence, lactic acidosis is well known to occur with metformin overdose (53–57), confirming that a potential for lactic acidosis does exist when there is marked metformin accumulation during therapeutic use.

Thus, guidelines prevent the use of metformin in many people who could benefit from it, even though there is substantial evidence that it is safe. Information on metformin pharmacokinetics in relation to GFR is scarce. One study reported decreased renal clearance in 5 T2DM patients with impaired renal function (31). Another study in 15 people with varying degrees of renal insufficiency examined metformin pharmacokinetics after a single 850 mg dose and found decreased renal excretion and prolonged $t_{1/2}$ compared to controls (58). Both the small number of subjects and the fact that pharmacokinetics were measured after a single dose limit the value of this study. Bardin, et al. attempted to develop a pharmacokinetic model by measuring metformin concentrations in 105 T2DM patients. They found that metformin clearance was negatively correlated to serum creatinine but did not propose a specific dosing schedule for people with reduced renal function. The study was limited by the fact that relatively few of the participants had impaired renal function, and kinetic calculations were based on an average of one fasting and one post-dose plasma metformin concentration (59). Thus, available data are insufficient to determine a safe and effective metformin dose schedule in people with T2DM and reduced GFR.

Heart Failure

Heart failure (HF), like CKD (and T2DM), is a disease of aging. Over 80% of annual deaths from HF occur in people aged >65 years (60). Half of all patients with HF have a preserved ejection fraction (HFpEF), and the prevalence of HFpEF is increasing by 1% per year (61). Analysis of data from previously published population-based studies (62; 63) indicates that 83% of all newly incident HF and 89% of newly incident HFpEF occurs after age 60 (VL Roger, personal communication). In addition to being older and hypertensive, people with HFpEF commonly display metabolic abnormalities; 40–75% are obese, over one-third are diabetic and many more have glucose intolerance (64–66). In a recently published population-based study, left ventricular stiffness was found to increase over a 4-year observation period in randomly selected, mostly non-diabetic individuals despite excellent control of blood pressure (67). The age-related increase in ventricular stiffness was correlated with increases in body mass, suggesting mechanistic relationship between adiposity and age-related ventricular stiffening. T2DM is associated with diastolic dysfunction and doubling of the risk of HF (68). The presence of T2DM portends for a poor prognosis in HF patients (69). In contrast to HF with low EF, *there is no effective treatment for HFpEF* (70). In subjects with and without HFpEF, the presence of obesity and T2DM are associated with abnormalities in myocardial energetics that likely contribute to resting diastolic dysfunction and loss of diastolic reserve with stress (71–73).

Recently there has been considerable interest in the effects of diabetes medication on the risk of HF. Poor glycemic control is associated with risk of hospitalization for HF (74), but this does not necessarily indicate a causal relationship. Particular concern has been expressed about the use of thiazolidinediones because of the sodium retention that occurs when these agents are given (75). Insulin therapy is associated with a 140% increase in the relative risk of developing HF (76). An increase in HF risk with insulin therapy could be due to weight gain and attendant increases in blood pressure (77; 78) and/or the antinatriuretic effect of insulin (79).

An intriguing literature has accumulated regarding the relationship between metformin use and HF. For more than 10 years after its approval in the United States, HF was an official contraindication for metformin use. The surprisingly common use of metformin in Medicare patients with HF has been attributed to lack of physician awareness of risks or a belief that the risks are overstated (80); HF is considered by many to be at least a relative contraindication to metformin use (81; 82). However, studies designed specifically to investigate outcomes in patients taking metformin tell a different story. As stated earlier, the risk of lactic acidosis does not appear to be increased by metformin use (51). Interestingly, the FDA, which added HF as a contraindication to metformin use several years after it was made available for use in the United States (83), subsequently concluded that metformin rarely, if ever, causes lactic acidosis (84). In late 2006, because of reassuring data regarding the safety of metformin in patients with HF, the FDA rescinded the contraindication (85). However, its use is still discouraged in the package insert: (http://packageinserts.bms.com/pi/pi_glucoophage.pdf).

Several studies indicate that metformin may actually be beneficial for patients with HF. Newly incident HF is reduced in people with T2DM on metformin (76; 86), and both death and hospitalization are lower in patients on metformin taken alone or in combination with sulfonylureas compared to those on sulfonylurea monotherapy (87). A retrospective cohort study of 16,417 Medicare beneficiaries with diabetes discharged after hospitalization for HF found a 31% decrease in one-year mortality in people treated with metformin compared with those who were treated with other agents (88). A recent analysis of nearly 20,000 people with diabetes in the REACH registry also demonstrated a 31% lower HF mortality in individuals taking metformin compared with those not taking it (12). Thus, 5 large studies unanimously demonstrate a relationship between metformin treatment and improved HF outcomes. These epidemiological observations are supported by research in animals. In diabetic mice, myocardial AMP-activated protein kinase (AMPK) and LV systolic function are depressed, and chronic metformin therapy produces significant improvement in both (89). There are no prospective studies of the use of metformin in HF in humans.

The mechanism by which metformin might have a favorable effect on HF is not known, but it may be related to decreased energy intake. Unintentional weight loss, as occurs in cardiac cachexia, has adverse prognostic implications in end-stage HF (90). However, we have found in a further analysis of data from a recently published study (67) that weight loss is associated with a decrease in vascular stiffness and abrogation of the normal age-related increase in LV stiffness (B. Borlaug, unpublished results). Indeed, intentional weight loss produced by bariatric surgery actually improves systolic and diastolic function, both in the

presence and absence of HF (91). A more modest weight loss, similar to that produced by metformin treatment, may also have favorable effects. In a study conducted by Italian investigators, a six-month lifestyle intervention produced a ~5% *intentional* weight loss in 34 people with HF (30% of whom had diabetes) accompanied by significant improvement in NYHA functional class, left ventricular (LV) EF, and perceived quality of life (92).

It is possible that weight loss decreases cardiac demand, since myocardial oxygen consumption (mVO_2) increases and myocardial efficiency ($work \div mVO_2$) decreases as body mass index increases (93). Myocardial dependence on fat oxidation (which is less energetically efficient than carbohydrate oxidation (94)) has been described in animal models of obesity (95). In obese humans with HF, weight loss results in decreased stroke volume, cardiac output and mVO_2 (96). The effect of metformin on mVO_2 is not known, but the decrease it produces in myocardial fatty acid oxidation (50) would be consistent with a reduction in global O_2 consumption by the heart. Relatively little information is available regarding the effects of metformin on diastolic function. Metformin improved diastolic function in diabetic rats (97), but did not have an effect on diastolic function measured by MRI in resting humans (50). It should be emphasized that measurements of diastolic function at rest are highly insensitive, and may fail to detect clinically meaningful changes that are demonstrable during the physiologic stress of exercise, where patients typically experience symptoms (98). Invasive hemodynamic stress testing has never been employed to evaluate possible effects of metformin on diastolic function in humans. Thus, the effect of metformin on diastolic function in HF is unknown.

Sympathetic activity (SA) is increased in HF (99; 100), and its magnitude correlates negatively with survival (101). In a study using MRI and MR spectroscopy to measure cardiac function and metabolism, van der Meer randomized 78 people with T2DM to receive metformin or pioglitazone. Metformin (but not pioglitazone) decreased cardiac index and cardiac work, with borderline decreases in stroke volume and LV mass plus decreases in myocardial glucose uptake and FFA oxidation (50). These findings are consistent with a decrease in myocardial SA and could be due to the generalized decrease in SA associated with a decrease in energy intake (102). However, little direct information is available regarding effects of metformin on SA in humans. Manzella, et al. demonstrated an increase in heart rate variability in obese diabetic subjects and interpreted the results as indicating decreased cardiac SA (103). However, heart rate variability is an unreliable indicator of SA (104). A study using microneurography found no effect of metformin on sympathetic nerve traffic in individuals with T2DM (105). Unfortunately, this study was limited by use of a submaximal metformin dose (1700 mg/day) for only 6 weeks in only 6 subjects, with no effect of metformin on insulin sensitivity. If metformin decreases SA, the mechanism could involve decreased food intake, which is known to occur with metformin therapy (21). Norepinephrine (NE) spillover, a marker of SA, increases with meals (106). Insulin is a known activator of the sympathetic nervous system (107), and metformin therapy reduces the rise in postprandial insulin concentrations (108). Negative energy balance is associated with a decrease in NE spillover (109) and a decrease in cardiac work and myocardial fatty acid uptake (110).

Conclusions

Metformin is currently the drug of choice for T2DM, and its primacy in the treatment of this condition is not likely to change because of its excellent safety record and unique CV benefits. Concerns about the safety of this agent because of lactic acidosis risk have proven to be largely unfounded; these concerns are likely due to holdover anxiety related to lactic acidosis caused by phenformin, which was in use in the United States from 1959 to 1977. As a result of a perceived risk of lactic acidosis, there has been reluctance to use metformin in patients with CKD. In fact, there is substantial evidence that metformin could be used safely in people with CKD-3 and eGFR values as low as 30 mL/min/1.73m². However, additional pharmacokinetic data are needed in order to develop a dosage scheme for people with CKD-3.

There is also considerable evidence that metformin can be used safely in patients with HF. Large epidemiological studies demonstrate an association between metformin treatment and improved HF outcomes. The mechanism for a salutary effect on metformin on HF, if it exists, is unknown, but possibilities include improvement in diastolic function and decreased cardiac work/demand related to decreased sympathetic activation. Prospective, randomized studies of metformin use in HF patient are needed.

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Figure 1.
Plasma metformin concentrations before and for 4 hours after a morning metformin dose (1000 mg) in a patient chronically taking 1000 mg twice daily (unpublished data).

Table 1

Range of serum creatinine concentrations in people with CKD-3 (eGFR 30 to 59 ml/min/1.73 m²)

Age	Non-black males	Non-black females	Black males	Black females
40	1.5–2.6	1.2–2.0	1.7–2.9	1.3–2.3
50	1.4–2.4	1.1–1.9	1.6–2.7	1.3–2.3
60	1.3–2.3	1.1–1.8	1.5–2.6	1.2–2.0
70	1.3–2.1	1.0–1.7	1.4–2.4	1.1–1.9
80	1.2–2.0	1.0–1.6	1.4–2.3	1.1–1.8

From the National Kidney Foundation GFR calculator, see http://www.kidney.org/professionals/kdoqi/gfr_calculator.cfm