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Monitoring Patients on Metformin: Recent Changes and Rationales

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Abstract

Objective: The Food and Drug Administration recently updated metformin prescribing recommendations for patients with diabetes and renal disease. The American Diabetes Association as well as the American Association of Clinical Endocrinologists and American Clinical Endocrinologists also recommend periodic monitoring of vitamin B_{12} levels for patients using metformin. A review of the literature was conducted to assess data to evaluate the recent updates to metformin usage and provide rationales for these recommendations. **Data Sources:** PubMed MESH terms "Diabetes Mellitus, Type 2" and "Renal Insufficiency, Chronic" and "Metformin" were searched with an English limitation from 1990 to May 2017. A MEDLINE search was conducted using the terms "metformin" and "renal disease" from 1990 to May 2017. A PubMed search was conducted using the MESH terms "vitamin b12 deficiency" and "metformin" from 1970 to May 2017. A MEDLINE search was conducted using terms "metformin" and "vitamin B12 deficiency" with an English limitation from 1970 to May 2017. **Study Selection and Data Extraction:** Retrospective and prospective clinical trials, meta-analyses, and systematic reviews were considered for inclusion. Citations from identified articles were also reviewed for inclusion. **Data Synthesis:** The incidence of metformin-associated lactic acidosis is minimal. Data indicate metformin-treated patients with an estimated glomerular filtration rate above 30 mL/min/1.73 m^2 have a reduction in mortality. Additionally, data suggest metformin may lead to vitamin B_{12} deficiency. **Conclusion:** Data support recommendations for metformin use in patients with diabetes and renal insufficiency with an estimated glomerular filtration rate above 30 mL/min/1.73 m^2. Data also suggest that baseline and periodic testing of vitamin B_{12} levels are warranted and supported by clinical guidelines due to the risk of vitamin B_{12} deficiency in metformin-treated patients.

Keywords

diabetes, type 2 diabetes, antihyperglycemics, acid-base balance

Background

Metformin was first approved for use in the United States in 1995.[1] Since 2006, it has been considered first-line therapy according to the American Diabetes Association (ADA) and European Association for the Study of Diabetes.[2,3] The American Association of Clinical Endocrinologists and American College of Endocrinology (AACE/ACE) also support metformin as first-line therapy for patients with type 2 diabetes.[4] Many new drug classes have been approved in the past several years. Despite the availability of these new agents, metformin continues to be the first-line agent for type 2 diabetes mellitus (T2DM). A recent meta-analysis by Maruthur and colleagues was designed to assess the comparative effectiveness and safety of thiazolidinediones, metformin, sulfonylureas, dipeptidyl peptidase-4 inhibitors, sodium-glucose cotransporter 2 inhibitors, and glucagon-like peptide-1 receptor agonists.[5] Investigators established that cardiovascular mortality was lower among metformin than sulfonylureas users, hemoglobin A1c reduction was similar across all drug classes with the exception of dipeptidyl peptidase-4 inhibitors, and body weight was maintained with metformin.[5] Researchers concluded that, after assessing the available drug classes, metformin is still suited to stand as first-line therapy due to its ability to lower A1c, limited adverse event profile, and benefits on cardiovascular outcomes.[5] Recently, the Food and Drug Administration (FDA) changed prescribing recommendations regarding the use of metformin in patients with renal disease.[6] Additionally, according to the 2017 ADA Standards of Medical Care in Diabetes and the 2017 AACE/ACE management algorithm, recommendations to periodically screen for vitamin B_{12} deficiency in those treated with metformin are present.[2,4]

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Data Sources

In order to describe the rationale for the recent changes, a PubMed search was conducted using the MESH terms "Diabetes Mellitus, Type 2" and "Renal Insufficiency, Chronic" and "Metformin" with an English limitation. A MEDLINE search was conducted using the terms "metformin" and "renal disease" with an English limitation. Searches were conducted from 1990 to May 2017. To gather data behind the vitamin B_{12} monitoring, a PubMed search was conducted using the MESH terms "vitamin b12 deficiency" and "metformin" with an English limitation. A MEDLINE search was conducted using terms "metformin" and "vitamin B12 deficiency" with English limitation. Searches were conducted from 1970 to May 2017. Retrospective and prospective clinical trials, meta-analyses, and systematic reviews were considered for inclusion. Citations from identified articles were also reviewed for inclusion. Additionally, citations from identified articles were reviewed for inclusion.

Reduced Renal Function

Phenformin, buformin, and metformin are the 3 agents that have been developed in the biguanide class.[7] Buformin was not widely used, but phenformin was used extensively until its withdrawal from the market in the 1970s due to its risk of lactic acidosis.[7] Although rare, metformin has been reported to be associated with lactic acidosis as well.[8]

The exact mechanism behind metformin-associated lactic acidosis is unknown.[9] It is theorized that the accumulation of metformin leads to an inhibition of mitochondrial complex I activity, which leads to a reduction in the production of adenosine triphosphate.[9,10] This reduction in available energy limits gluconeogenesis, and adenosine monophosphate-activated protein kinase is activated.[9,10] Activated adenosine monophosphate-activated protein kinase does 2 things: first it leads to glycolysis, which leads to an increase in lactate; second, it stimulates fatty-acid β-oxidization, which releases ketone bodies.[9] The imbalance in the 2 acids, ketone bodies and lactate, lead to lactic acidosis.[9] Interestingly, patients with diabetes and patients treated with metformin have been reported to have a similar incidence of lactic acidosis, 6/100 000 person years.[11]

Risk factors for metformin-associated lactic acidosis include renal dysfunction, sepsis, alcohol abuse, liver failure, radiologic contrast media administration, and conditions associated with hypoxemia—acute myocardial infarction, unstable or acute congestive heart failure, and shock.[12-15] When metformin was approved in 1995, it was approved with its use contraindicated in some patients with renal disease or dysfunction due to concerns of lactic acidosis.[8] Until recently, in the United States, it was recommended that metformin be avoided in patients with a serum creatinine of >1.4 mg/dL in women and >1.5 mg/dL in men. Some believe these restrictions and the caution behind the use of metformin is due to the prior experience with phenformin and not directly related to metformin itself.[16]

Metformin Use in the Setting of Contraindications

Despite the restrictions in place, there is substantial evidence indicating prescribers have continued to use metformin in patients with contraindications.[16-23] The Diabetes Audit and Research in Tayside Scotland/Medicines Monitoring Unit (DARTS/MEMO) investigators performed a retrospective cohort study evaluating patients with T2DM in the Tayside, Scotland, region from January 1993 to June 1995.[16] The investigators' purpose was to determine how many patients receiving metformin had a contraindication to the drug.[16] There were 691 patients who developed contraindications to metformin therapy and only 10% were discontinued from therapy.[16] Renal dysfunction, defined as 2 recordings of serum creatinine >1.7 mg/dL, on different days within 4 weeks, occurred in 88 patients, of whom 22 (25%) discontinued therapy.[16] Despite the high number of patients treated with metformin in the presence of contraindications, only one episode of lactic acidosis occurred.[16] This patient was 72 years old and developed an acute myocardial infarction, acute renal failure, and lactic acidosis.[16] The DARTS/MEMO investigators believe this case of lactic acidosis was due to the extensive myocardial infarction.[16]

A cross-sectional analysis in Germany was conducted evaluating patients from January 1, 1995, to May 31, 1998, who were treated with metformin in an outpatient setting. They found 73% of the 308 patients had a contraindication or risk factor warranting metformin's discontinuation.[20] Contraindications included 25% with heart failure, 1.3% with liver impairment, 6.5% with respiratory insufficiency, and 19% with renal impairment. Renal impairment was defined as an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2.[20] The average creatinine clearance in these patients was 38.5 mL/min with a range from 14.9 to 59.8 mL/min.[20] Other patients had risk factors including advanced coronary heart disease, atrial fibrillation, chronic alcohol abuse, peripheral vascular disease, and pregnancy.[20] Despite the high number of contraindications, no cases of lactic acidosis were seen.[20]

Kennedy and Herman evaluated baseline parameters of the patient planned to be randomized into the Glycemic Optimization with Algorithms and Labs at Point of Care (GOAL A1c) study.[21] More than 4800 patients were identified as receiving metformin prior to study entry, and 219 (4.5%) had serum creatinine values above FDA-recommended restrictions.[21] When calculating the eGFR, it was found that 13.4% of men and 17.7% of women had an

Table 1. REACH Registry's Metformin Mortality Results.[25]

eGFR, mL/min/1.73 m^2	Total Number of Patients, n	Total Number Treated With Metformin, n (%)	Mortality Risk Among Metformin Users, Adjusted HR (95% CI)
≤60	10 768	4442 (40.7%)	0.89 (0.71-1.11)
30 to <60	5031	1572 (31.2%)	0.64 (0.48-0.86)
<30	590	118 (20%)	1.06 (0.47-2.38)

Abbreviations: eGFR, estimated glomerular filtration rate; HR, hazard ratio; CI, confidence interval.

eGFR <60 mL/min/1.73 m^2.[21] Study investigators conclude their findings are consistent with other studies, which indicate metformin continues to be used in patients with contraindications.

Safety in Reduced Renal Function

Although contraindications are present, the previously mentioned studies indicate prescribers have continued to use metformin even in these settings.[16-23] In order to evaluate the safety of metformin in those with a reduced renal function, several studies have been published assessing these concerns.[13,24-26]

Rachmani et al set out to evaluate the appropriateness of the contraindications to metformin therapy in a prospective randomized controlled trial.[13] To be included in the study, patients were between the age of 40 and 75, developed diabetes after age 40, and had a body mass index of 24 to 40 kg/m^2. Patients treated with metformin were followed prospectively until they developed a contraindication to therapy, including a renal contraindication defined as serum creatinine 1.49 to 2.49 mg/dL. Four hundred seventy-one patients were screened, and 393 were included in the analysis. Patients were randomized to either continue metformin therapy or discontinue therapy in response to their newly developed contraindication. Baseline serum lactic acid level was 27 mg/dL in both groups, and baseline serum creatinine was similar in both groups ranging between 1.82 and 1.84 mg/dL. Patients were followed for 4 years. At the end of the study, serum lactic acid was very similar between groups: 29.4 mg/dL in those with metformin discontinued and 29.9 mg/dL in those continued on metformin. A multivariable analysis revealed that the only factors influencing serum lactate level were serum creatinine and body mass index. There were no reported cases of lactic acidosis.[13]

The Fremantle study was a longitudinal, observational, cross-sectional study of those individuals living in the Fremantle, Australia, area.[27] Of those recruited, 1294 had T2DM. The Fremantle study examined the ethnic and racial differences in the presence of serum antibodies including glutamic acid decarboxylase and ICA512/IA-2.[27] In a separate publication, they utilized the data gathered from the Fremantle study to assess the relationship between metformin use, its contraindications, and the incidence of lactic acidosis.[24] During the 13.2-year follow-up, there were a total of 5 cases of lactic acidosis, corresponding to an incidence of 40/100 000 (13-94) patient-years.[24] Two cases of lactic acidosis occurred in those with diabetes not treated with metformin, an incidence of 28/100 000 (3-100) patient-years.[24] Three cases occurred in those with diabetes treated with metformin, an incidence of 57/100 000 (12-168) patient-years.[24] The study concludes, on the basis of the similar incidences of lactic acidosis, that metformin does not increase the risk of lactic acidosis even in the setting of renal insufficiency.[24]

The Reduction of Atherothrombosis for Continued Health (REACH) Registry investigators assessed whether metformin use was associated with a difference in mortality after adjustment for baseline differences.[25] They were also assessing the propensity to receive metformin among patients with established coronary artery disease, cerebrovascular disease, or peripheral arterial disease.[25] In this study, REACH Registry investigators evaluated only patients with type 1 or type 2 diabetes mellitus, defined as taking an antihyperglycemic medication, and a history of arterial disease.[25] Mortality rates were lower among all metformin users at 6.3% (95% confidence interval [CI] = 5.2% to 7.4%) than nonusers at 9.8% (95% CI = 8.4% to 11.2%).[25] Investigators examined the total number of patients and total number treated with metformin in those with renal insufficiency broken down as mild, moderate, and severe.[25] In each group, they assessed mortality risk among those treated with metformin (see Table 1).[25] Investigators found a nonsignificant trend toward mortality benefit in those treated with metformin and an eGFR ≤60 mL/min/1.73 m^2.[25] A significant mortality benefit was seen in those with an eGFR 30 to <60 mL/min/1.73 m^2.[25] A significant reduction in mortality was not seen in patients with severe renal dysfunction, defined as an eGFR below 30 mL/min/1.73 m^2, but as evidenced by the wide confidence interval, this group may not have been sufficiently powered.[25] Authors from this study conclude that metformin used in secondary prevention of cardiovascular disease (CVD) can be beneficial in preventing mortality.[25] Moreover, this study indicates that it can also provide mortality prevention in patients with a history of CVD and renal insufficiency.[25]

Ekström et al evaluated the Swedish National Diabetes Register to determine the safety and efficacy of metformin in

patients with T2DM and varying levels of renal function.[28] To be included in the study, participants were aged 40 to <85 years and must have been treated with continuous glucose lowering treatment for 12 months.[28] Participants were included between 2004 and 2007 and followed until an end point occurred or until 2010.[28] Patients had a mean age of 65 years, mean diabetes duration of 9.4 years, and a mean HbA1c of 7.3%.[28] Insulin and oral antihyperglycemic agents in any combination were compared with that of metformin for the incidence of CVD, infection or any acidosis, and all-cause mortality across 3 subgroups of renal function: eGFR ≥60 mL/min/1.73 m^2, eGFR 45 to <60 mL/min/1.73 m^2, and eGFR 30 to <45 mL/min/1.73 m^2.[28] Metformin had a lower incidence of any acidosis and serious infection in the eGFR 45 to <60 mL/min/1.73 m^2 and eGFR ≥60 mL/min/1.73 m^2 groups, adjusted hazard ratio (HR) = 0.85 (95% CI = 0.74 to 0.97) and adjusted HR 0.91 (95% CI = 0.84 to 0.98), respectively.[28] Metformin was also associated with a reduction in all-cause mortality in the eGFR ≥60 mL/min/1.73 m^2 group with an adjusted HR 0.87 (95% CI = 0.81 to 0.94).[28] These subgroup analyses did not reveal any increased risk of CVD, any acidosis or serious infection, or all-cause mortality from metformin monotherapy.[28]

A Cochrane review was completed to evaluate the incidence of lactic acidosis in those treated with metformin compared with those not treated with metformin.[29] Data were gathered from 347 studies including randomized controlled trials and observational studies from 1959 to 2009. There were no cases of fatal or nonfatal lactic acidosis in the 70 490 patient-years of metformin users or in the 55 451 patients-years of the non-metformin group.[29]

As evidence by the Cochrane review, the risk of lactic acidosis is extremely rare and some would even call into question if it is a concern health care providers should have when utilizing the drug, given its rare occurrence.[28] The aforementioned studies have indicated that metformin can be used safely in those with serum creatinine higher than the previously recommend cut points of 1.4 mg/dL and 1.5 mg/dL and an eGFR <60 mL/min/1.73 m^2.[13,16,20,24,25,28] In those with reduced renal function, metformin has not only been found to be safe but evidence indicates, as cited above, it may reduce the risk of mortality, any acidosis, and severe infection.[28]

There is also concern if the use of serum creatinine is the best measurement of renal function. Evidence indicates serum creatinine may underestimate the renal function in females and the elderly.[30] Warren et al evaluated the potential impact of eGFR instead of serum creatinine cut points to determine metformin eligibility.[30] The analysis was done in the Lothian region in Scotland. Current local guidelines at that time recommended against the use of metformin if serum creatinine was >1.7 mg/dL.[30] Patients obtained from a national registry in the past 15 months were included if they had T2DM and a serum creatinine from 0.45 to 12.44 mg/dL. A total of 19 924 patients were identified to meet criteria. Of the 11 789 taking metformin, 95.8% had a serum creatinine <1.7 mg/dL. As classified by the National Kidney Foundation stages, 6379 (56.5%) taking metformin were in stage 2 with an eGFR 60 to 89 mL/min/1.73 m^2 and 2880 (25.5%) were in stage 3 with an eGFR 30 to 59 mL/min/1.73 m^2.[30] No patients treated with metformin were in stage 4 or 5. Allowing those with an eGFR >36 mL/min/1.73 m^2 would result in 263 (1.3%) patients with creatinine ≤1.7 mg/dL becoming ineligible for metformin therapy, and 241 (1.2%) patients with creatinine >1.7 mg/dL becoming newly eligible.[30] The use of an eGFR >40 mL/min/1.73 m^2 would have 560 (2.8%) patients with creatinine ≤1.7 mg/dL becoming ineligible for metformin therapy and 102 (0.5%) patients with creatinine >1.7 mg/dL becoming eligible.[30]

In 2012, Dr Flory submitted a citizens' request to the FDA requesting a change in the metformin labeling with regard to metformin use in patients with renal insufficiency.[31] Specifically, Dr Flory requested the contraindication to metformin not apply to those with an eGFR >30 mL/min/1.73 m^2.[31] In 2013, Drs Lipska and Inzucchi of Yale University also wrote a citizen petition to the FDA recommending a modification of the labeling regarding the renal contraindication for metformin.[32] They recommend metformin be contraindicated in those with an eGFR <30 mL/min/1.73 m^2. In those with an eGFR 30 to 45 mL/min/1.73 m^2, they recommend continuing metformin use and monitoring renal function every 3 to 6 months.[32] When prescribing metformin to an individual with an eGFR 30 to <45 mL/min/1.73 m^2, they recommend using prescribing with caution and utilizing a lower dose, up to half maximum recommended dose while monitoring renal function every 3 months.[32]

In response to the evidence of continued use in renal insufficiency and its safety in doing so, as well as the citizens' petitions, the FDA made the decision to change the renal restrictions on the use of metformin in mild to moderate kidney disease.[6] They now recommend the use of eGFR instead of serum creatinine to determine if a patient with reduced renal function can safely take metformin. The new recommendation states metformin is contraindicated in patients with an eGFR <30 mL/min/1.73 m^2.[6] Those with an eGFR between 30 and 45 mL/min/1.73 m^2 should not be initiated on metformin.[6] If a person's eGFR falls between 30 and 45 mL/min/1.73 m^2 and they are already treated with metformin, their provider should assess their risk and benefit associated with continued use (Table 2).[6] The ADA state the FDA's recommendation on the use of metformin in their guidelines.[2] The AACE/ACE consensus statement on diabetes management are in agreement with the FDA's statement with one variation.[4] AACE/ACE recommend a reduced dose of metformin in those with an eGFR between 30 and 45 mL/min/1.73 m^2.[4]

After metformin's labeling was updated, Crowley and colleagues set out to further assess the consequences or benefit the expanded labeling will have.[33] A systematic review was performed to assess the benefits and harms of

Table 2. FDA Metformin Recommendation.[6]

eGFR 30 to 45 mL/min/1.73 m^2	Do not start metformin. If currently treated with metformin, determine risk and benefits of continued use.
eGFR <30 mL/min/1.73 m^2	Discontinue metformin

Abbreviation: FDA, Food and Drug Administration; eGFR, estimated glomerular filtration rate.

metformin use in patients with moderate to severe chronic kidney disease (CKD), congestive heart failure (CHF), and chronic liver disease.[33] Cochrane Library, EMBASE, MEDLINE from January 1994 to September 2016, and International Pharmaceutical Abstracts from January 1994 to November 2015 were searched to obtain the data.[33] After review of 532 full-text articles, 17 were identified to be eligible for inclusion.[33] Six of those studies included patients with moderate to severe CKD.[33] When assessing mortality, there was a 22% lower risk in those patients with moderate to severe CKD receiving metformin than those who were not receiving it (HR = 0.78 [95% CI = 0.63-0.96]; $Q = 29.7$ [$P < .001$]; $I^2 = 79.8\%$).[33] The 2 studies that reported mortality based on the stage of CKD found those with an eGFR from 30 to <45 mL/min/1.73 m^2 saw less benefit than those with an eGFR 45 to <60 mL/min/1.73 m^2.[33] A benefit in mortality was also seen in patients with CHF (HR = 0.78 [CI = 0.71-0.87]; $Q = 26.6$ [$P = .003$]; $I^2 = 62.3\%$) and chronic liver disease (n = 250; HR = 0.43 [CI = 0.24-0.78]), even regardless of cirrhosis severity.[33] There was no difference in major adverse cardiac events, defined as myocardial infarction, angina, stroke, and procedures, between those with an eGFR of 45 to <60 mL/min/1.73 m^2 (n = 6655; HR = 0.94 [95 % CI = 0.84-1.05]) and those with an eGFR of 30 to <45 mL/min/1.73 m^2 (n = 1894; HR = 1.00 [95% CI = 0.83-1.19]).[33] Metformin use was found to be associated with a lower rate of CHF readmission (HR = 0.87 [95% CI = 0.78-0.97]; $Q = 11.7$ [$P = .009$], $I^2 = 74.3\%$).[33] The authors also found a significant reduction in readmission rate for patients treated with CHF and CKD when treated with metformin (n = 5859; HR = 0.91 [CI = 0.84-0.99]).[33] This systematic review further reinforced the appropriateness of the label change indicating the benefits seen from metformin use outweigh the harm.[33]

Vitamin B_{12} Monitoring

Vitamin B_{12} is found in animal proteins and cannot be manufactured by the body.[34,35] It is a required component of normal neurologic function, red blood cell production, and DNA synthesis.[35] One of the most commonly considered manifestations of vitamin B_{12} deficiency is macrocytic megaloblastic anemia.[34,35,36] It has been found that patients can have reduced levels of vitamin B_{12} without signs of anemia; therefore, screening of a vitamin B_{12} level is important, even when hemoglobin and hematocrit are within normal range.[34,35,37] Other manifestations seen from vitamin B_{12} deficiency are listed in Table 3.[34-36]

Table 3. Manifestations From Vitamin B_{12} Deficiency.[34-36]

Hematologic
Macrocytic megaloblastic anemia
Integumentary
Hyperpigmentation
Vitiligo
Gastrointestinal
Glossitis
Jaundice
Autonomic nervous system
Orthostatic hypotension
Erectile dysfunction
Urinary incontinence
Neuropsychiatric
Cognitive impairment
Ataxia of gait
Irritability
Peripheral neuropathy
Weakness

Vitamin B_{12} is found bound to protein in animal food products.[38] On ingestion, gastric acid and pepsin in the stomach free up the vitamin B_{12}. After its removal from food, it is bound to R-binder, a glycoprotein in gastric fluid that protects vitamin B_{12} from the harsh acidic environment of the stomach. Then it moves into the duodenum where pancreatic protease degrades R-binder from the R-binder–vitamin B_{12} complex. Free vitamin B_{12} is then bound to intrinsic factor (IF), a glycosylated protein secreted by gastric parietal cells. Absorption of vitamin B_{12} occurs at the ileum of the small intestines. At the ileal cell, IF-vitamin B_{12} binds to cubilin receptor forming IF-vitamin B_{12}-cubilin receptor complex. Calcium is required in this binding process to strengthen the binding. The ileal enterocyte then endocytose the IF-vitamin B_{12}-cubilin receptor complex. IF-vitamin B_{12} detaches from cubilin. In the ileal cell, a lysosome is formed. In the lysosome, IF is broken down, and vitamin B_{12} is allowed to move freely into the serum (Figure 1).[38]

Since the early 1970s, vitamin B_{12} deficiency has been reported with metformin use.[39,40] This incidence of vitamin B_{12} deficiency in those treated with metformin is reported as high as 9.5% to 31%.[39,41-48] There is some concern in interpreting the incidence reported from these studies, as there is wide variation in the literature as to the definition used for vitamin B_{12} deficiency. The exact mechanism is unknown, but it is theorized that metformin antagonizes the calcium cation and thus interferes with the process allowing vitamin B_{12} to be absorbed into the circulation.[47]

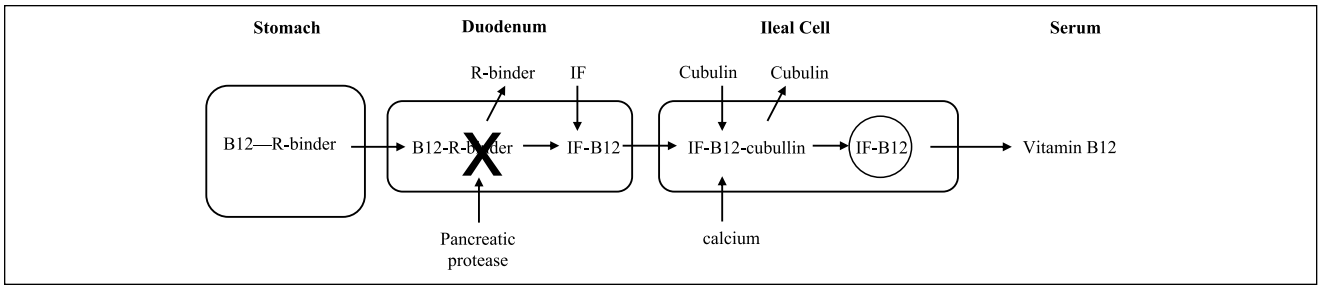

Figure 1. Absorption of vitamin B_{12}.[36]

Chapman et al performed a systematic review and meta-analysis of the published data to determine the association between metformin and vitamin B_{12} deficiency in patients with diabetes mellitus.[49] Vitamin B_{12} deficiency was defined as a serum vitamin B_{12} level of <204 pg/mL and borderline deficiency as a level of 204 to 299 pg/mL. Twenty-five studies were included in the systematic review.[49] Most studies indicated that those treated with metformin had a lower serum vitamin B_{12} level.[49] In the systematic review, the Hyperinsulinemia: the Outcome of its Metabolic Effects (HOME) trial was analyzed.[49] In this prospective multicenter randomized control trial, patients were randomized to metformin 850 mg 3 times a day or placebo.[49,50] In the 16-week post-randomization phase, a greater reduction in vitamin B_{12} level was seen in those treated with metformin than placebo, −14% (95% CI = −4.2% vs −24%; $P < .0001$).[49,50] By end of study after a 4-year period, a further reduction was seen in vitamin B_{12} level, −19% (95% CI = −24% to −14%; $P < .001$).[49,50] A significantly greater number of absolute vitamin B_{12} deficiency (serum concentration <204 pg/mL) was seen in the metformin group compared with placebo ($P = .004$) and the corresponding number needed to harm was 13.8 per 4.3 years.[49,50] In the meta-analysis portion of Chapman's publication, 4 studies were included.[49] Duration of the studies included were short at less than 4 months.[49] The authors state the mean difference in serum B_{12} levels suggest that taking metformin for 6 weeks to 3 months leads to a statistically significant reduction in B_{12} concentration by 77 pg/mL.[49] This meta-analysis is limited by the short duration.[49] Based on the small number of studies included, a funnel plot to assess publication bias could not be calculated.[49] Additionally, due to the small number of studies included, this study is not assessing as many patients as are generally seen in meta analyses.[49]

Risk Factors

In the evaluation of potential risk factors for metformin-induced vitamin B_{12} deficiency, it seems dose of metformin and duration of use are two of the greatest risk factors for its development.[46-48,51,52] Ko and colleagues assessed the prevalence of vitamin B_{12} deficiency in a Korean population seen at a diabetes center.[46] Potential risk factors for metformin-induced vitamin B_{12} deficiency were also assessed.[46] The authors found duration of metformin and higher doses of metformin had the greatest association.[46] Duration of 4 to <10 years had an odds ratio (OR) of 4.65 (95% CI = 2.36-9.16) and duration of 10 or more years an OR of 9.21 (95% CI = 3.38-25.11).[46] Daily metformin dose ranges of 1000 to <2000 mg had an OR of 2.52 (95% CI = 1.27-4.99) and doses at or above 2000 mg had an OR of 3.8 (95% CI = 1.8-7.92).[46] In Ting et al's analysis, patients with a year's worth of computer medical record that used a Hong Kong laboratory were included in an analysis to assess for the risk factors of metformin-induced vitamin B_{12} deficiency.[51] They found daily dose of metformin, per 1000 mg increment had an adjusted OR of 2.88 (95% CI = 2.15-3.81) and use of metformin for more than 3 years had an adjusted OR 1.99 (95% CI = 1.30-3.05), reinforcing the findings of Ko and colleagues.[51]

In the Diabetes Prevention Program (DPP) study, patients with impaired glucose tolerance were randomized to metformin 850 mg twice daily, placebo, or an intensive lifestyle program.[52] Patients were followed-up for a mean of 3.2 years.[52] At the end of DPP, all participants were offered participation in the follow-up study, DPP Outcomes Study.[52] In the DPP Outcomes Study, those originally assigned to metformin in DPP received metformin at the same dose until diabetes developed or they reached an A1c of at least 7% at which time they were sent to their physician for management.[52] Vitamin B_{12} and homocysteine levels were collected at an average of 5 and 13 years after initial randomization.[52] Total metformin-years of exposure was the only significant predictor of vitamin B_{12} deficiency found in this analysis.[52] The adjusted OR for metformin-associated B_{12} deficiency per year of metformin use was 1.13 (1.06-1.20).[52] Beulens and colleagues evaluated the possible risk factors for metformin-associated vitamin B_{12} deficiency and found patients treated with a higher dose and higher cumulative dose of metformin were more likely to have vitamin B_{12} deficiency.[53]

Defining and Treating Vitamin B_{12} Deficiency

Vitamin B_{12} deficiency is generally defined as a vitamin B_{12} level <150 pg/mL, although sometimes patients with higher levels who have symptoms of vitamin B_{12} deficiency may

Table 4. Factors Affecting Vitamin B_{12}, Homocysteine, And Methylmalonic Acid Levels.

Falsely normal vitamin B_{12} levels	Falsely low vitamin B_{12}
Renal insufficiency	Oral contraceptive use
Liver disease	Multiple myeloma
Myeloproliferative disorders	Pregnancy
	Folate deficiency
Falsely elevated homocysteine	Falsely elevated methylmalonic acid
Folate deficiency	Renal insufficiency
Levodopa therapy	Volume depletion
Renal insufficiency	

benefit from treatment.[35] In symptomatic patients with a low-normal vitamin B_{12} level, between 200 and 350 pg/mL, obtaining a methylmalonic acid or serum homocysteine level can be helpful in ruling out the diagnosis.[34-36] Normal methylmalonic acid is defined as <0.28 mmol/L and normal homocysteine can range from 5 to 15 mmol/L.[54] If an elevation is seen in either, a definitive diagnosis of vitamin B_{12} deficiency can be made. Methylmalonic acid and serum homocysteine have been proven to be highly sensitive for the diagnosis of vitamin B_{12} deficiency.[35] Methylmalonic acid is equally sensitive but more specific than serum homocysteine; therefore, when possible, it preferred for confirming the diagnosis.[35] Certain factors can lead to variations in vitamin B_{12}, methylmalonic acid, and homocysteine levels, as described in Table 4.[34,35]

As some of the manifestations of vitamin B_{12} deficiency can occur as complications of diabetes, it is important to properly evaluate a patient treated with metformin for vitamin B_{12} deficiency to assure it is not the cause of such concerns. The neurologic manifestations from untreated vitamin B_{12} deficiency can be irreversible, so identification and treatment is prudent.[36] Treatment of vitamin B_{12} can be by oral or intramuscular route. A Cochrane review set out to determine the difference in efficacy of oral versus intramuscular vitamin B_{12}.[55] Randomized controlled trials that randomized participants to oral or intramuscular vitamin B_{12} to treat vitamin B_{12} deficiency were included in the analysis.[55] Two studies were found to meet criteria and were included in the analysis. In the Kuzminski study, participants were randomized to receive cyanocobalamin 1 mg intramuscularly on days 1, 3, 7, 10, 14, 21, 30, 60, and 90 or 2 mg orally on a daily basis for 120 days.[56] In the Bolaman study, participants were randomized to receive 1000 µg cobalamin orally once daily for 10 days or 1000 µg intramuscularly once daily for 10 days.[57] After 10 days, both treatments were administered once a week for 4 weeks, and after that, once a month for life.[57] Kuzminski et al found that the oral group had higher serum vitamin B_{12} concentration at 2-month and 4-month follow-up.[56] Bolaman et al did not analyze the difference in serum vitamin B_{12} between groups but reported both groups had a statistically significant increase, $P < 0.001$, in serum vitamin B_{12} concentration from day 0 to day 90.[57] The authors conclude from this review that oral supplementation with vitamin B_{12} may be as efficacious as intramuscular vitamin B_{12} in achieving a hematologic response.[55]

Some consider treating patients with vitamin B_{12} prophylactically to prevent the development of deficiency in those who are at risk.[35] It is unknown if prophylactic supplementation with cyanocobalamin would prevent development of vitamin B_{12} deficiency in metformin-treated patients.[35] What has been clear in recommendation is prophylactic treatment of vitamin B_{12} deficiencies in patients undergoing gastric bypass surgery.[35]

Conclusion

Despite the many years metformin has been available on the market, new changes continue to occur regarding its use and monitoring. As the aforementioned data have indicated, prescribers should begin using eGFR cut points to determine the appropriateness of metformin therapy in patients with renal dysfunction. In patients with an eGFR of 30 to 45 mL/min/1.73 m^2, the FDA recommends metformin use should be continued with an increased frequency of monitoring of renal function. In those with an eGFR <30 mL/min/1.73 m^2, metformin should not be used. The available data indicate metformin can continue to provide a reduction in mortality, even in those with an eGFR from 30 to 60 mL/min/1.73 m^2. As metformin increases the risk of vitamin B_{12} deficiency, a serum level should be obtained to monitor for its development, data suggest particularly in those treated with high doses of metformin, greater than 1000 mg/day, and those treated for an extended duration, greater than 3 years.

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