Assessment of Metformin Intolerance: A Retrospective Chart Review

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Abstract

Objective: The aim of the present study is to determine similarities between patients with type 2 diabetes not on metformin therapy compared to patients on metformin therapy at a resident-led primary care clinic. *Methods:* An exploratory, single-center retrospective chart review was performed on patients 18 years and older with a documented diagnosis of type 2 diabetes seen at the University of Arkansas for Medical Sciences Family Medicine Clinic in Little Rock, Arkansas. Of the 2452 patients who met criteria for the study, 1085 patients did not have a documented metformin allergy. A subset of 216 patients who were not currently prescribed metformin and had no documented metformin allergy were further examined and compared to the 869 patients who were prescribed metformin. We sought to determine reasons for nonuse by evaluating their EPIC electronic health record. Information on these patients such as race, gender, hemoglobin A1c (A1c), kidney function, stated metformin intolerance, and comorbid disease states such as neuropathy, chronic kidney disease (CKD), ulcerative colitis, and irritable bowel syndrome were collected. Further examination was performed to determine why patients were not on metformin therapy and potential similarities between metformin intolerant patients. *Results:* The results of the study indicated a significant difference between metformin users and non-users in relation to body mass index (BMI) and diagnosis of CKD. Metformin non-users were found to have significantly lower mean BMI (30.87 vs. 35.43; p-value <0.0001), and significantly higher rates of CKD (25.93% vs 14.73%; p-value <0.0001) as compared to metformin users. BMI value of patients (coefficient: 0.2033, p value: <0.0001) was found to be significantly and positively correlated with metformin use, and CKD (coefficient: - 0.1191, p-value: <0.0001) was found to be significantly and negatively correlated with metformin use. A1c levels for patients not on metformin therapy were evaluated. Most non-metformin patients fell in prediabetic A1c levels ranging from 5-6.4% (84 patients; 38.89%), and 31 patients (14.35%) should be on insulin therapy according to guidelines. *Conclusion:* The results demonstrated that patients with lower BMI, CKD, or A1c in the prediabetic range were less likely to be prescribed metformin.

Keywords: metformin, intolerance, type 2 diabetes, adverse, counseling

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Background:

Of the 37 million Americans living with diabetes, over 90% are diagnosed with type 2 (1). A recommended first-line pharmacotherapy agent for type 2 diabetes is metformin (2). Metformin is usually initiated early in patients with type 2 diabetes unless they have contraindications to the drug such as severe renal impairment or acute/chronic metabolic acidosis including diabetic ketoacidosis. Metformin has high success with correcting hyperglycemia, and it is thought to potentially decrease diabetes-related complications such as cardiovascular disease (3,4). Metformin has also been shown to significantly decrease hemoglobin A1c (A1c) levels by around 1.3% in patients treated with metformin monotherapy (5). Compared with other diabetes medications, metformin carries a relatively low side effect profile with low risk for hypoglycemia. The most common side effects tend to be gastrointestinal (GI).

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Metformin acts as an oral antihyperglycemic agent in the biguanide class. While the exact mechanisms of action of the drug are not fully understood, metformin prevents the liver from converting fats and amino acids to glucose through gluconeogenesis. It also activates the enzyme AMP- activated protein kinase (AMPK), which increases cell responsiveness to insulin and uptake of glucose from the blood (6).

Despite its success and importance, only 50-70% of patients diagnosed with type 2 diabetes take metformin in conjunction with other diabetes medications (7). The most common reason reported for failure to continue metformin therapy is the GI intolerance associated with the drug. Patients may experience transient GI side effects such as diarrhea, nausea, flatulence and abdominal discomfort. However, in some patients, these side effects do not improve and they may not be able to tolerate the drug. Intolerance affects up to 25% of patients treated with metformin and often leaves those patients unable or unwilling to use this pharmacotherapy (8). Patients suffering from metformin intolerance most commonly report mild to severe symptoms of GI upset including abdominal pain, constipation, dyspepsia, nausea, vomiting, bloating, flatulence, and diarrhea (9). GI intolerance is often confused with a true metformin allergy. True metformin allergy is extremely rare and

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most often presents as leukocytoclastic vasculitis and psoriasiform drug eruption (10). GI intolerance is often transient and subsides if drug therapy is reintroduced, while a true allergy has persistent internal and external manifestations that require that the drug be stopped immediately (10).

Varying demographics have been studied investigating and providing hypotheses as to what patient factors may contribute to intolerance. Previous findings show that GI intolerance likely occurs without respect to age or race of the patient (11). It has been shown that GI intolerance in females is significantly higher than in males (11, 12). Hypotheses to why this may be include the idea that GI intolerance is less transient in women than in men, strategies for limiting intolerance are not sufficiently applied for women, and that women simply report GI intolerance more frequently than males (12). When looking to offset intolerance in female patients, it is recommended that females be given a lower starting dose than their male counterparts (11, 12).

Offsetting metformin intolerance in patients is best done by starting at a low dose and titrating up as tolerated. A common titration schedule increases doses every two weeks starting at 500 mg daily, then increasing to 500 mg twice daily, and finally 1000 mg twice daily. Eating with each dose can help prevent symptoms such as nausea and feeling ill. Intolerance can also be offset by using metformin extended release (XR). Metformin XR contains an outer hydrophilic layer that eliminates the burden of having to take pills multiple times daily and lowers the rate of therapy discontinuation due to GI side effects (9). A study examining the side effects of metformin XR found that rates of diarrhea, nausea, and vomiting were <10% (9).

Southern states have the highest prevalence of type 2 diabetes, with Arkansans falling at 12.4% of the adult population diagnosed with type 2 diabetes (13). This is the fourth highest of all states in America. Targeting the use of effective pharmacotherapy to treat and minimize the diabetes epidemic is essential to the health and wellness of our patient population. The aim of the present study is to determine similarities between patients who reported metformin intolerance in an urban family medicine clinic in central Arkansas to inform when more conservative metformin dosing strategies may need to be employed.

Methods:

This was an exploratory single-center, retrospective chart review. The research was approved by the Institutional Review Board at the University of Arkansas for Medical Sciences (UAMS). Data were identified and extracted from the Arkansas Clinical Data Repository (AR-CDR). Any data that could not be obtained in this manner were collected via chart review through EPIC electronic health records. All patients with a diagnosis of type 2 diabetes without complications (ICD-10-CM E11.9) who had an office visit at the UAMS Family Medical Center between 01/01/2014-12/31/2021 were reviewed for inclusion. Inclusion criteria included diagnosis of type 2 diabetes (ICD-10-CM E11.9), assigned a primary care physician at UAMS Family Medical Center, and an office visit within the study timeframe. Exclusion criteria were age <18 years and positive antibodies demonstrating presence of type 1 diabetes. For those with an active prescription for the maximum recommended dose of metformin two grams daily, no further analysis was performed to determine metformin intolerance. Those who had no active prescription for metformin or were prescribed a lower than maximum dose were analyzed further to determine if metformin intolerance or a reason for lower than maximum dose were documented.

Demographic data included age, sex, race, and gender. Clinical information obtained included body mass index (BMI), drug allergies and reaction, diagnosis of chronic kidney disease (CKD) (ICD-10-CM N18), renal function (eGFR and serum creatinine), B12 level, diagnosis of B12 deficiency (ICD-10-CM D51), diagnosis of neuropathy (ICD-10-CM codes G99, E11.40), presence of antibodies indicative of type 1 diabetes (e.g., glutamic acid decarboxylase, islet cell, insulin autoantibodies, or tyrosine phosphatase), C-peptide level, and diagnosis of other gastrointestinal disease (ICD-10-CM K50 [Crohn's disease], K51 [ulcerative colitis], K58 [irritable bowel syndrome]). The medical record number was also obtained so that chart notes could be reviewed for clinical reasoning associated with metformin discontinuation or continuation of suboptimal dose.

For patients with no documented metformin allergy who were not prescribed metformin, we sought to determine reasons for nonuse by evaluating their EPIC electronic health record and collecting data such as A1c, eGFR, and reason listed for patient not being on metformin therapy. Other pre-specified demographic data and clinical information were further examined to determine both why these patients were not on metformin therapy and potential similarities between metformin intolerant patients. Furthermore, patients with a documented metformin allergy were examined to document their other listed drug allergies. Cross-examination of drug allergies was performed to elucidate whether patients with metformin allergy were also likely to have an allergy to other medications. After determining similarities, we identified how the intolerance was managed, evaluated other listed drug intolerance or allergies, and assessed A1C's for those patients not on metformin.

The patient and clinical characteristics were compared between the two study groups using student's t-test for continuous variables and Chi-squared tests for categorical variables. Due to presence of low to zero counts in some categories, p-value and significance could not be tested for those specific categories. To assess the correlation between factors and no metformin use, Pearson correlation coefficients were generated. A1c levels

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between patients evaluated were displayed to assess disease control in patients. All analyses were performed using SAS statistical software (version 9.4; SAS Institute Inc, Cary, North Carolina). All p-values were significant at $\alpha \leq 0.05$.

Results:

Of the 2452 patients with a type 2 diabetes diagnosis, the final study sample consisted of 1085 patients who did not have any documented metformin allergy. From this sample, 216 patients were classified as metformin non-users and 869 were classified as metformin users (Table 1). Patients not on metformin therapy were found to have a significantly lower mean BMI (30.87 vs. 35.43; p-value <0.0001), and significantly higher rates of chronic kidney disease (CKD) (25.93% vs 14.73%; p-value <0.0001) as compared to metformin users. The two groups were similar with respect to all other covariates, including gender, age, race, vitamin B12 deficiency, neuropathy, ulcerative colitis, and irritable bowel syndrome. Of the patients not currently on metformin, 190 (87.96%) did not have metformin intolerance stated in chart, 14 patients (6.48%) did have intolerance stated, and 12 patients (5.56%) had no information on the topic.

The Pearson correlation coefficients are displayed in Table 2. The BMI values of patients (coefficient: 0.2033, p value: <0.0001) was found to be significantly and positively correlated with metformin use, and CKD (coefficient: - 0.1191, p-value: <0.0001) was found to be significantly and negatively correlated with metformin use. No other significant correlations were found in the analysis.

The A1c levels are shown in Table 3. Most patients evaluated who were not on metformin (84 patients; 38.89%) fell in the prediabetic range with A1c levels between 5-6.4%. There were 10 patients (4.63%) with a normal A1c below 5%, and 48 patients (22.22%) had a usual A1c goal for most diabetic patients falling between 6.5-8%. There were 11 patients (5.09%) not being controlled in clinic with an A1c between 8.1-9%, and 16 patients (7.41%) who did not have controlled blood glucose levels but did not yet need insulin with an A1c between 9.1-10%. A portion of our patient population (31 patients; 14.35%) had A1cs over 10% and should have been on insulin according to guidelines (14).

Discussion:

With metformin being one of the most cost-efficient medications used to treat type 2 diabetes, it is imperative that this medication is available to our patient population. Many patients in our clinic do not have insurance coverage, so more expensive injectables or oral therapies are not always available or accessible. Patients without true reason not to be on maximum dose metformin therapy should be evaluated and reconsidered for therapy. Some common reasons for patients not being on maximum dose metformin therapy include having CKD stage 3b or higher or having intolerance to the medication. One contraindication to metformin therapy is a diagnosis of CKD stage 4 or higher. Those with CKD stage 3B should not take the maximum dose but instead be limited to one gram daily. Metformin is entirely cleared by renal excretion, and patients with low kidney function cannot properly excrete metformin. We found that patients not on metformin therapy had significantly higher rates of diagnosed CKD than those prescribed metformin. However, of the patients not taking metformin, 74.04% did not have a documented diagnosis of CKD. Thus, many of our patients would still be indicated for metformin therapy if they had no other contraindications.

Another reason for patients not being on metformin therapy is an intolerance to the medication, such as GI disturbance. Of the patients we examined, 87% did not have intolerance to metformin stated in their chart. This could be due to patients not reporting their side effects, providers not properly documenting these reports, or that this side effect is not prevalent in the patient population we examined.

Our results found that patients not on metformin therapy had a significantly lower mean BMI than patients on metformin therapy. The BMI value of patients was found to be significantly and positively correlated with metformin use. These results could be due to patients being on other diabetic medications that have higher rates of weight loss association such as glucagon-like peptide (GLP-1) agonists or sodium glucose co-transporter 2 (SGLT-2) inhibitors, which are also indicated in patients with type 2 diabetes and CKD or heart failure and may preclude the use of metformin in these patients. This could also be due to other factors such as patients who are not on metformin therapy having controlled A1c rates that may be associated with lower body weight. While patients using metformin had higher BMI, this study was not designed to establish a correlation between metformin and BMI.

We evaluated A1c levels for patients not on metformin therapy and found that more than one-third (84 of 216; 38.89%) of our patients fell into the prediabetic range of A1c levels between 5-6.4% and 48 patients (22.22%) were within the usual A1c goal range of 6.5-8%. It is likely that these patients had higher A1c levels before they started on metformin therapy, and their A1c levels have since decreased in response to metformin therapy. We also found that there were 10 patients (4.63%) with a normal A1c below 5%, for whom metformin may not be necessary. There were a total of 58 (26.85%) patients whose A1c values were not at goal, who would have benefitted from additional antihyperglycemic therapy. Although additional therapy may be needed, the guidelines recommend continuing metformin along with these therapies, including insulin, if not contraindicated. Metformin works as an insulin sensitizer and improves glycemic control by enhancing liver insulin sensitivity. It also reduces hepatic gluconeogenesis and may improve muscle insulin sensitivity, which contributes to the proven

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benefits of using metformin and insulin together in diabetic patients.

Comparing patients not on metformin therapy to those receiving metformin showed that more non-metformin patients fell into the pre-diabetes range than those on metformin (38.89% vs 28.88%). This may have been due to their providers not prescribing metformin before a diagnosis of diabetes and choosing to recommend lifestyle modifications over medication therapy. There was a smaller percentage of patients in the non-metformin use group who were considered uncontrolled with an A1c greater than 8% (26.85% vs 34.75%).

Our data also revealed that black patients had the highest rates of metformin nonuse. It is unclear with our specific data set if they had higher rates of CKD or other contraindications that favored other antidiabetic therapies over metformin. Additional studies looking at our African American patients without metformin could be conducted to see if there are underlying factors within this patient population that exclude the use of metformin.

In addition to conducting future studies to find results to questions posed from this study, education for patients and providers should be increased at our clinic. Providers should be educated on proper charting of medication intolerances, metformin counseling to minimize side effects, and guidelines on when metformin therapy should or should not be initiated or discontinued. Since the electronic health record at our institution allows the documentation of an intolerance in the allergy section, with space for severity and a description of the reaction, this would be the most visible way to document a metformin intolerance. In addition, documenting in a chart note to provide more detail about the intolerance and strategies that were employed to try to minimize it would help ensure appropriate steps were taken. Patients should be educated on ways to take metformin and the importance of this drug therapy in the treatment of type 2 diabetes. Relaying information such as taking the medication with a full meal and water, titrating the medication up slowly to full dosage, utilizing maximally tolerating doses, employing the extended-release dosage form, and taking the medication consistently as prescribed can help reduce intolerance.

This study does have some acknowledged limitations. Limitations include being a single-center study, not having a comparison group, and missing data for some variables examined, such as race, intolerance stated in chart, and A1c. Other limitations to the study are the small sample size and the inability conclude if obesity contributes to metformin intolerance because of missing data.

Conclusion:

The results demonstrated that patients with lower BMI, diagnosed CKD, or A1c in the prediabetic range were less likely to be prescribed metformin. Since patients with uncontrolled type 2 diabetes without contraindications should be on metformin therapy, our study shows that our facility can work to improve charting patient intolerances and counseling on metformin use. An increase in education and training for both providers and patients will likely improve patient experience and increase the number of patients in our facility on effective metformin therapy.

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Conflict of Interest:

We declare no conflicts of interest or financial interests that the authors or members of their immediate families have in any product or service discussed in the manuscript, including grants (pending or received), employment, gifts, stock holdings or options, honoraria, consultancies, expert testimony, patents, and royalties.

Treatment of Human Subjects:

This project was approved by the University of Arkansas for Medical Sciences Institutional Review Board (IRB) through an Expedited Review Procedure

Disclaimer: The statements, opinions, and data contained in all publications are those of the authors.

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Table 1: Patient and Clinical Characteristics

Characteristics		No metformin use		Metformin use		p-value
Total sample		N=216		N=869		
Age (mean; SD)		50.75	15.99	50.14	12.91	0.5983
BMI (mean; SD)		30.87	8.01	35.43	8.93	<0.0001*
		N	%	N	%	
Race	White	73	33.80	232	26.7	0.1347
	Black	124	57.41	564	64.9	
	Asian	2	0.93	20	2.3	
	Other	13	6.02	40	4.6	
	Unknown/ missing	4	1.85	7	0.81	
Gender	Female	106	49.07	436	50.17	0.7726
	Male	110	50.93	433	49.83	
Intolerance stated in chart	No	190	87.96	NA		
	Yes	14	6.48			
	Missing	12	5.56			
	Unknown/ missing	16	7.41			
Chronic Kidney Disease	No	160	74.07	741	85.27	<0.0001*
	Yes	56	25.93	128	14.73	
Vitamin B12 Deficiency	No	215	99.54	865	99.54	0.9959
	Yes	1	0.46	4	0.46	
Neuropathy	No	182	84.26	723	83.2	0.7078
	Yes	34	15.74	146	16.8	
Esophagogastro-duodenoscopy	No	216	100.00	866	99.65	0.5134
	Yes	0	0.00	3	0.35	
Ulcerative Colitis	No	216	100.00	858	98.73	0.0859
	Yes	0	0.00	11	1.27	
Irritable bowel syndrome	No	214	99.07	860	98.96	0.8854
	Yes	2	0.93	9	1.04	

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Table 2: Pearson Correlation Coefficients

Pearson Correlation Coefficients Prob > |r| under H0: Rho=0	
Number of Observations	**Metformin use**
Gender	-0.00877
	0.7728
Chronic kidney disease	-0.11914
	<.0001*
Neuropathy	0.01138
	0.7081
Age at first T2DM encounter	-0.01821
	0.549
BMI	0.20333
	<.0001*

Table 3: A1c levels of patients with no metformin use

A1c %	**No metformin use** **Total: 216** **n (%)**	**Metformin use** **Total: 869** **n (%)**
Missing	16 (7.41)	19 (2.19)
<5	10 (4.63)	10 (1.15)
5-6.4	84 (38.89)	251 (28.88)
6.5-8	48 (22.22)	287 (33.02)
8.1-9	11 (5.09)	79 (9.09)
9.1-10	16 (7.41)	69 (7.94)
>10	31 (14.35)	154 (17.72)

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