(RESEARCH ARTICLE)

Use of metformin in the management of colorectal cancer: A survey

Ta`Ceana Montgomery [1], Bisrat Hailemeskel [1] and Fekadu Fullas [2, *]

[1] College of Pharmacy, Howard University, 2300 4th Street, Washington D.C., 20059, USA.
[2] Pharmacy Department, Unity Point Health-St. Luke's Hospital, 2720 Stone Park Boulevard, Sioux City, IA 51104, USA.

Abstract

A survey was conducted among 42 Howard University first year professional pharmacy students regarding their knowledge and opinions about the use of metformin in colorectal patients. Twenty-five (59.5%) respondents agreed that metformin reduces the risk of colorectal cancer in type 2 diabetes patients, and the majority (n=22, 52.4%) disagreed with the statement that metformin is a drug recommended for colorectal cancer. Twenty-five (59.5%) replied that colorectal cancer is a common illness regardless of age range. Twenty-four (57.1%) survey participants responded in favor of patients taking metformin to lower the risk of colon cancer. On the other hand, the majority (n=25, 59.5%) agreed that colorectal patients with diabetes mellitus taking metformin have the same outcome as those who do not have diabetes. In response to the opinion part of the questionnaire, the majority (n=23, 54.7%) admitted to feeling comfortable about recommending metformin to increase the chance of survival of colorectal patients, while only 18 (42.8%) were confident in explaining the benefits of metformin in preventing colorectal cancer. Twenty-three (54.7%) of respondents prefer natural and holistic methods, and 16 (28.1%) knew someone with type 2 diabetes who was taking metformin for the prevention of colorectal cancer. Most respondents (n=29, 69%) believe prescription medications should be used to prevent colorectal cancer rather than metformin which has inadequate supporting evidence. A sub-analysis appears to indicate that female participants, those with previous pharmacy-related jobs, and those with fewer years of work experience disagree with most of the opinion questions compared to their counterparts. They also had a wider range of opinions among themselves compared to their counterparts.

Keywords: Metformin; Colorectal Cancer; CRC; Type 2 Diabetes; Survey; Likert Score

1. Introduction

Metformin is an old anti-diabetic drug that has been dubbed "the aspirin of the twenty-first century." [1]. Just like aspirin, it is a synthetic derivative of the natural products galegine or/and guanidine obtained from the plant *Galega officinalis* which was in use in medieval Europe [2]. Colorectal cancer (CRC) is the third most common cancer in men and the second most common cancer in women. Risk factors increase with age, and they vary by sex and race/ethnicity [3]. Metformin is a component of many herbal therapeutic substances, known since 1500 BCE in Egyptian medicine [1]. The function of metformin is to lower intestinal absorption and hepatic glucose production.

Metformin, in addition to its blood sugar lowering effect, has several other medical benefits that are non-approved by the FDA. One such use is in the management of non-alcoholic fatty liver. Use of metformin in patients with nonalcoholic fatty liver disease significantly improved median survival rates when compared to patients who didn't take metformin and did not increase the risk of liver injury or lactic acidosis. The median survival of diabetic patients with any etiology of cirrhosis receiving metformin (n=172) was significantly greater compared with patients who discontinued

---

* Corresponding author: Fekadu Fullas

Pharmacy Department, UnityPoint Health-St. Luke's Hospital, 2720 Stone Park Boulevard, Sioux City, IA 51104, USA.
Current address: 1409 Jackson Rd, Silver Spring, MD 20904, USA.

metformin (*n*=78; 11.8 vs 5.6 years). Among subgroup of patients with nonalcoholic steatohepatitis (NASH), metformin continuation (*n*=98) reduced the risk of death by 67% compared with metformin discontinuation (*n*=44; median survival, 12.1 vs 5.1 years) [4]. Another potential use of metformin is its beneficial effect in patients with polycystic ovary syndrome (PCOS). PCOS is a complex disorder of the endocrine system characterized by hyperandrogenism and chronic anovulation after other disorders have been excluded [5]. In women with PCOS, metformin was found to improve insulin sensitivity was associated with a decrease in circulating androgen levels, improved ovulation rates, and improved glucose tolerance. The American College of Obstetricians and Gynecologist (ACOG) recommends clomiphene citrate to be the first-line treatment option for ovulation induction for women with PCOS who are attempting to conceive. However, in obese women, there may be an increase in pregnancy rates when metformin is added to a clomiphene regimen [6].

Metformin has also been found to be beneficial in mitigating weight gain secondary to antipsychotic therapy. Metformin, compared with placebo, significantly reduced mean weight change and BMI in adult and pediatric patients taking antipsychotics for schizophrenia or schizoaffective disorder. The difference in mean weight change with metformin was greater in first episode patients compared with chronic patients who had already gained weight [7].

An emerging epidemiological, pre-clinical, and clinical evidence supports the use of metformin as a cancer therapeutic. This benefit is associated with its ability of lowering circulating insulin. Hyperinsulinemia seems to be associated with one of the root causes of malignancy. Metformin may exhibit direct inhibitory effects on cancer cells by inhibiting mammalian target of rapamycin (mTOR) signaling and protein synthesis [8]. Other studies have reported the benefits of metformin in CRC patients. A positive trend was demonstrated in patients taking metformin with an observation of a marked improvement of CRC survival rate, specifically in patients with diabetes [9]. One report reviewed the mortality rate in patients with CRC coupled with diabetes. The authors concluded that CRC patients with diabetes receiving metformin had lower mortality rate than those not receiving metformin [10].

2. Methods

This study enrolled 44 first year professional pharmacy students from Howard University College of Pharmacy. Of these, 42 completed the survey, with a 95.5% response rate. The survey was optional, and it was distributed to students during a drug information course. All questions, demographics, and responses were analyzed using Qualtrics. Survey questions consisted of 8 demographic, 5 knowledge-based and 5 opinion questions. Likert score scale was used to collect data (1=strongly agree; 2=agree; 3=disagree and 4=strongly disagree). A mean score was computed for each of the knowledge-based and opinion related questions. Demographic data, including age, gender, state of residence, work experience, annual income, and education were collected. All results were analyzed by using standard statistical methods. Significance was determined by a chi-square (χ^2) test.

3. Results and discussion

Most of the survey participants were female (*n*=27, 64.3%) (Table 1 & Figure 1). Relatively, the highest number of respondents reported an age range of 24 to 26 years (*n*=17, 40.5%). About 81% (*n*=34) of the participants had a bachelor's degree before joining the pharmacy program (Table 1 & Figure 2). Prior to starting the pharmacy program, the majority (*n*=24, 57.1%) lived in the Maryland/Virginia/Washington D.C. metropolitan area. Half of the participants had worked full-time. Sixteen (38.1%) worked in pharmacy-related job areas. During their employment, nearly 31% of the survey participants had earned less than USD 10,000 per year. Prior to starting pharmacy training, the majority had worked for 1 to 4 years (Table1).

Twenty-five (59.5%) respondents agreed that metformin reduces the risk of colorectal cancer in type 2 diabetes patients. The majority (*n*=22, 52.4%) disagreed with the statement that metformin is a drug recommended for colorectal cancer. Twenty-five (59.5%) thought that colorectal cancer is a common illness affecting all age groups. Twenty-four (57.1%) survey participants agreed patients take metformin to lower the risk of colon cancer. Most (*n*=25, 59.5%) agreed that colorectal patients with colorectal diabetes mellitus taking metformin have the same outcome as those who do not have diabetes (Table 2). On the opinion questionnaire statements (Table 3), the majority (*n*=23, 54.7%) felt comfortable about recommending metformin to increase the chance of survival of colorectal patients, while only 18 (42.8%) were confident in explaining the benefits of metformin in preventing colorectal cancer. Twenty-three (54.7%) of respondents prefer natural and holistic methods, and 16 (28.1%) knew someone with type 2 diabetes who was taking metformin for the prevention of colorectal cancer. Most respondents (*n*=29, 69%) believe prescription medications should be used to prevent colorectal cancer rather than metformin with little supportive evidence.

In a sub-analysis, female participants seem to have a higher disagreement rate with most survey questions than male their counterparts (Likert score 2.3 vs. 2.1). They also have a wider range of opinions than the male counterparts (standard deviation [SD] of 4.65 vs 4.51). However, the difference was not significant (p=0.3245). Survey respondents who had pharmacy-related jobs previously tend to disagree more in most of the opinion questions relative to those who never worked in health care settings (Likert score 2.45 vs. 2.11; p <0.0001). Those who had had pharmacy related jobs also have a wider range of opinions among themselves compared to their counterparts (SD= 5.19 vs. 3.89 vs. 4.26). A difference was also noted in participants who had different years of previous work experience. Those who have less than 2 years of work experience seem to disagree with most of the opinion questions than those who had over 2 years of work experience (mean score of 2.36 vs. 2.00 vs. 2.22 respectively; p-value 0.0373). They also have a wider range of experiences (SD= 5.13 vs. 4.2 vs. 3.78).

In the knowledge-based part of the survey, over 50% of the survey respondents had the correct responses to three out of the five questions (Table 2). Considering that they are first-year students, their level of knowledge was fair in the three questions. On the other hand, they fared lower in the other two questions with an average 40.5% correct response rate.

Table 1 Demographic characteristics of respondents

Characteristics	Respondents (n, %)	95% CI (% range)[1]
Age (years)		
21-23	14 (33.3)	19.1-47.6
24-26	17 (40.5)	25.6-55.3
27-29	5 (11.9)	2.1-21.7
>29	6 (14.3)	3.7-24.9
Gender		
Male	15 (35.7)	21.2-50.2
Female	27 (64.3)	49.8-78.8
Education		
Some college	1 (2.4)	0.0-7.0
Associate Degree	1 (2.4)	0.0-7.0
BA/BSc	34 (81)	69.1-92.8
MSc	4 (9.5)	2.7-22.6
PhD/Professional	2 (4.8)	0.0-11.2
Residence		
Washington, D.C.	4 (9.5)	0.7-18.4
Maryland	13 (31)	16.9-44.9
Virginia	7 (16.7)	5.4-27.9
Other States	18 (42.9)	27.9-57.2
Working now		
Yes	9 (21.4)	9.0-33.8
No	33 (78.6)	66.2-90.9
Work experience		
Never worked	2 (4.8)	0.0-11.2
Short-term	3 (7.1)	0.0-14.9

Part-time	16 (38.1)	23.4-52.8
Full-time	21 (50)	34.9-65.1
Type of job		
Pharmacy related	16 (38.1)	23.4-52.8
Other healthcare	12 (28.6)	14.9-42.2
Non-health related	13 (31)	16.9-44.9
Not applicable	1 (2.4)	0.0-7.0
Annual income		
< USD 10,000	13 (31)	16.9-44.9
10,001-20,000	7 (16.7)	5.4-27.9
20,001-30,000	6 (14.3)	3.7-24.9
30,001-40,000	5 (11.9)	2.1-21.7
>40,000	11 (26.2)	12-9-39.5
Years worked		
None	1 (2.4)	0.0-7.0
1-2	19 (45.2)	30.2-60.3
3-4	11 (26.2)	12.9-39.5
>4	11 (26.2)	12.9-39.6

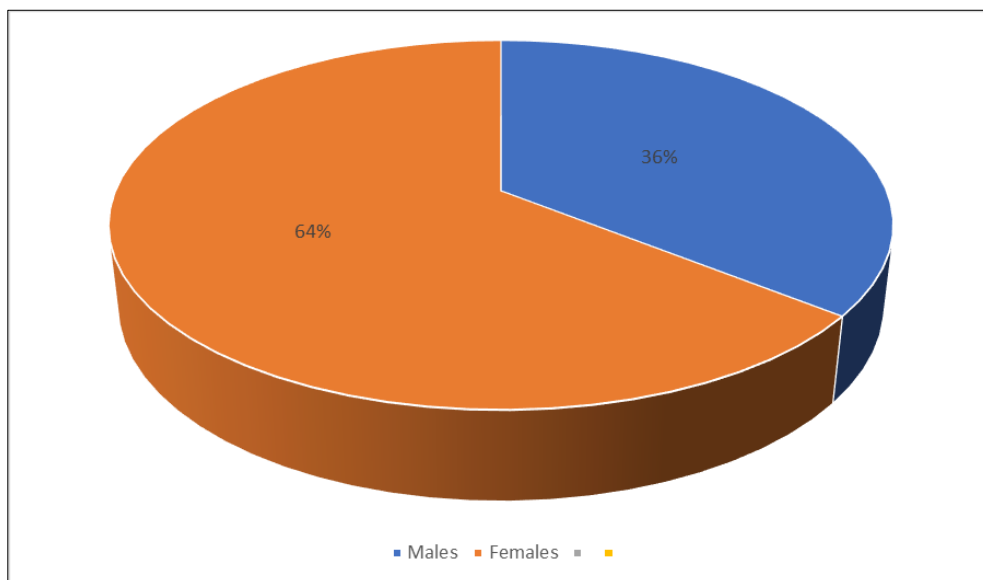1CI = Confidence Interval; normal approximations of binomial exact values.
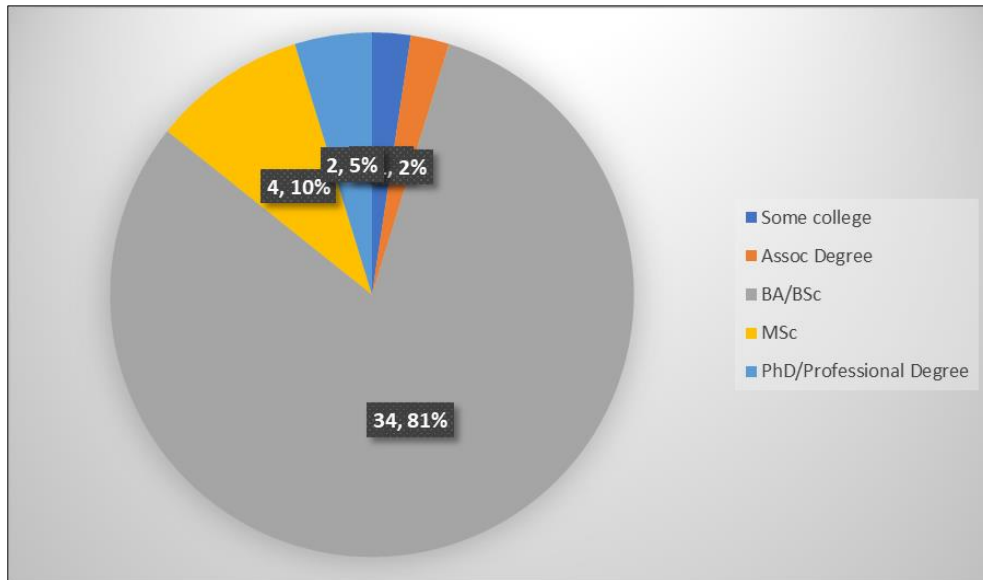

Figure 1 Gender of Survey Participants

Figure 2 Prior Education Level

Table 2 Responses to knowledge-related survey questionnaire statements

	Survey Statement*	Response [*n*, (%)]						LK (m ±SD)
		SA	A	DA	SDA	TA	TDA	
1.	Metformin reduces the risk of colorectal cancer (CRC)	12	13	16	1	25*	17	2.14±0.87
		(28.6)	(30.9)	(38.1)	(2.4)	(59.5)	(40.5)	
2.	CRC is a common illness regardless of age	11	14	16	11	25	17*	2.17±0.85
		(26.2)	(33.3)	(38.1)	(2.4)	(59.5)	(40.5)	
3.	Patients with CRC & diabetes mellitus (DM) generally have the same outcome from using metformin as patients who are not diabetic	6	19	15	2	25	17*	2.31±0.78
		(14.3)	(45.2)	(35.7)	(4.8)	(59.5)	(40.5)	
4.	Metformin is one of the first drugs recommended for CRC	10	10	19	3	20	22*	2.36±0.93
		(23.8)	(23.8)	(45.2)	(7.1)	(47.6)	(52.4)	
5.	Patients with Type 2 DM who take metformin have a lower risk of CRC	7	17	15	3	24*	18	2.33±0.85
		(16.7)	(40.4)	(35.7)	(7.1)	(57.1)	(42.9)	

Abbreviations: SA=strongly agree; A=agree; DA=disagree; SDA=strongly disagree.; TA=total agree; TD=total disagree; LK= Likert score; m ± SD=mean ± standard deviation.; *Correct answers: n (%): 25 (59.5) for 1; 17 for 2 (40.5); 17 for 3 (40.5); 22 (52.4) for 4; 24 (57.1) for 5.

Table 3 Responses to opinion-related survey questionnaire statements

Survey Statement	Response [*n*, (%)]						LK (m ±SD)
	SA	A	DA	SDA	TA	TDA	
I feel comfortable recommending metformin because it helps improve the chance of survival form colorectal cancer (CRC)	6 (14.3)	17 (40.5)	14 (33.3)	5 (11.2)	23 (54.8)	19 (45.2)	2.43±0.89
I feel confident explaining the benefits of metformin in preventing CRC	4 (9.5)	14 (33.3)	18 (42.9)	6 (14.3)	18 (42.9)	24 (57.1)	2.62±0.85
I prefer using natural and holistic methods over chemically produced medications such as metformin	8 (19.1)	15 (35.7)	15 (35.7)	4 (9.5)	23 (54.8)	19 (45.2)	2.36±0.91
I personally know someone who has Type II DM who is also using metformin for prevention of CRC	5 (11.9)	11 (26.2)	16 (38.1)	10 (23.8)	16 (38.1)	26 (61.9)	2.74±0.96
I believe we should use prescription drugs that are well known to prevent CRC rather than metformin with little evidence to support its use	12 (28.6)	17 (40.5)	6 (14.3))	7 (16.6	29 (69.1)	13 (30.9)	2.19±1.04

Abbreviations: SA=strongly agree; A=agree; DA=disagree; SDA=strongly disagree. TA=total agree; TD=total disagree; LK= Likert score; m ± SD=mean ± standard deviation

4. Conclusion

A survey among 42 HU first year pharmacy students regarding their knowledge and opinions about the role of metformin in the management of colorectal cancer revealed mixed results. In the knowledge-based part of the survey, over 50% of the survey respondents had the correct responses to three out of the five questions, while only 40% had the correct knowledge about the other three questions. The strongest correct opinion was expressed (*n*=28, 69%) on using only well-known drugs for preventing colorectal cancer rather than metformin. A sub-analysis of the data appears to indicate female participants, those with previous pharmacy-related jobs, and those with fewer years of work experience disagree with most of the opinion questions than their counterparts. They also had a wider range of opinions among themselves compared to their counterparts. Considering that they are first-year students, the level of knowledge of the survey participants was generally adequate.

Compliance with ethical standards

Approval

The survey was approved by Howard University IRB as part of a Drug Information course given by one of us (BH).

Statement of informed consent

This survey was conducted as part of HU College of Pharmacy drug information course offered by one of us (BH); therefore, it didn't require informed consent of survey participants.

References

[1] Pourmatroud E. Metformin in Health Issues and Reproductive System. In Metformin; IntertechOpen: Rijeka, Croatia, 2019. [Google Scholar] Cross Ref] [Green Version].

[2] Grahame HD. 4.12. A New Understanding of Metformin. In Comprehensive Pharmacology (ed: Terry Kenakin); Elsevier, Amsterdam, 2022, pp 280-200. (https://www.sciencedirect.com/science/article/pii/B9780128204726000992) https://doi.org/10.1016/B978-0-12-820472-6.00099-2.

[3] Pande M, Frazier ML Epidemiology. In Colorectal Cancer: Diagnosis and Clinical Management (eds: John H. Scholefield and Cathy Eng); John Wiley & Sons Ltd, New Jersey, 2014, pp 1-26. https://doi.org/10.1002/9781118337929.ch1.

[4] Zhang X, Harmsen WS, Mettler TA, et al: Continuation of metformin use after a diagnosis of cirrhosis significantly improves survival of patients with diabetes. Hepatology 2014; 60 (6): 2008-2016.

[5] Libby G, Donnelly LA, Donnan PT, Alessi DR, Morris AD, Evans JM. New users of metformin are at low risk of incident cancer: a cohort study among people with type 2 diabetes. Diabetes Care. 2009, 32: 1620-1625. 10.2337/dc08-2175.

[6] ACOG Committee on Practice Bulletins - Gynecology: ACOG Practice Bulletin No. 108: Polycystic ovary syndrome. Obstet Gynecol 2009; 114(4):936-949.

[7] de Silva VA, Suraweera C, Ratnatunga SS, et al. Metformin in prevention and treatment of antipsychotic induced weight gain: a systematic review and meta-analysis. BMC Psychiatry 2016; 16(1):341.

[8] Dowling RJ, Goodwin PJ, Stambolic V. Understanding the benefit of metformin use in cancer treatment. BMC Med. 2011 Apr 6;9:33. doi: 10.1186/1741-7015-9-33. PMID: 21470407; PMCID: PMC3224599.

[9] Spillane S, Bennett K, Sharp L, Barron TI. A cohort study of metformin exposure and survival in patients with stage I-III colorectal cancer. Cancer Epidemiol Biomarkers Prev. 2013 Aug;22(8):1364-73. doi: 10.1158/1055-9965.EPI-13-0347. Epub 2013 Jun 10. PMID: 23753040. Available from: https://pubmed.ncbi.nlm.nih.gov/23753040/ (accessed 2022 Nov 8).

[10] Lee JH, Kim TI, Jeon SM, Hong SP, Cheon JH, Kim WH. The effects of metformin on the survival of colorectal cancer patients with diabetes mellitus. Int J Cancer. 2012; 131:752-759. https://doi.org/10.1002/ijc.26421.