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Metformin associates with lower on colorectal neoplastic risk in African American diabetic patients

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Abstract

Metformin, a biguanide class of anti-diabetic drugs, not only may reduce primary cancer risk, but might also be an effective therapy with chemotherapy regimens for recurring colorectal cancers. The aim of this study was to evaluate the association between Metformin therapy and colorectal neoplasia among type 2 diabetic mellitus African American patients. We reviewed the medical records of 3950 patients underwent diagnostic colonoscopy from 2000 to 2012. Diabetic patients with and without colon neoplastic lesions (cases and Controls, respectively) were evaluated for their drugs (Metformin and Insulin) usage. Patients in this study were evaluated in two groups: diabetic patients diagnosed with colorectal neoplasia (Cases) and diabetic patients without colorectal neoplastic lesions (Controls). The median duration of diabetes was 5 years in controls *vs.* 4.5ys in the case group. Controls were more on Metformin as compared to patients in the case (60% *vs.* 43%; P=0.02). There were no difference between single therapy with Metformin and combination therapy of Metformin and Insulin. Median duration of Metformin in control paients were 2 years vs 1 year in the case group. Multivariate logistic regression adjusted for age and gender demonstrated that patients on Metformin for more than 5 years had less neoplastic lesion when compared to patients on Metformin less than 5 years (OR=0.2(95% CI 0.1-0.4), P=<0.001). Patients on Metformin had lower rate of colorectal neoplastic lesions. As such, Metformin might have a protective effect that can be capitalized on for the treatment and prevention of colorectal neoplastic lesions.

Introduction

Patients with type 2 Diabetic Mellitus patients (DM) are at increased risk for colorectal neoplastic lesions such as colorectal adenomas and cancer [1]. The main reason for high colorectal cancer risk in patients with DM is endogenous hyperinsulinemia. In Diabetic patients who are suffering from cancer, worse cancer outcomes are encountered [2]. Furthermore, epidemiological data support an association between excess body weight and DM with an increased risk of colon cancer in males [3]. The American Diabetes Association reported that 13.2% of all African Americans aged 20 years or older were diagnosed with diabetes in 2014. African Americans are 1.7 times more likely to have diabetes than non-Hispanic whites [4].

Insulin resistance and hyperinsulinemia have been associated with increased risk of several types of neoplasm and specifically with colorectal cancer [5-7]. Insulin therapy also was associated with more colorectal neoplastic lesions incidence [8].

In patients with type 2 DM, metformin reduced the incidence of adenomas transform into CRC. Therefore, metformin may be useful for the prevention of CRC in patients with type 2 DM. Metformin, a biguanide class of anti-diabetic drugs, not only may reduce primary cancer risk, but also can be effective therapy with chemotherapy regimens for recurring colorectal cancers [8,9]. Metformin reduces hepatic glucose output and circulating glucose levels, which leads to a decline in circulating insulin levels [10]. In vitro and animal studies indicate that metformin prevents colorectal cancer (CRC). Potential molecular mechanisms of metformin may be due to inhibiting mammalian targets of rapamycin (mTOR) signaling, protein synthesis and its direct inhibitory effects on cancer cells [11].

Here, we analyzed the association between metformin usage and risk of colorectal neoplasia in African Americans, a population at high risk for both CRC and DM.

Materials and methods

Patients

In this retrospective study, we reviewed the medical records of 3950 patients with diagnostic colonoscopy from 2000 to 2012 at Howard University Hospital. Two hundred four diabetic patients were selected from these patients. Diabetes diagnosis was confirmed by an endocrinologist, based on Fasting Blood Sugar levels (FBS) ≥ 126 or one Random Blood Sugar levels (RBS) ≥ 200 with symptoms or HbA1c ≥ 6.5 and 5 years history of DM. We categorized diabetic patients with colorectal neoplastic lesions (adenoma, polyps, and cancers) as cases and diabetic patients with normal colonoscopy as controls. Clinic-Pro software was used to extract medication history including; Metformin and Insulin. The study was approved by Howard University Institutional Review Board (IRB).

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Statistical analysis

Demographic and clinical variables including type of treatment were compared between cases and controls using Student's t-test or Chi-square test. We assessed the effect of metformin and insulin on neoplastic colonic lesions in multivariate logistic regression adjusted for age and gender. Furthermore, we stratified these analyses based on duration of treatment. All analyses were performed by STATA 13.0 (StataCorp., College Station, TX).

Results

Male DM patients displayed more colonic lesions

Among 204 diabetic patients, 156 (76%) had colon neoplastic lesions (cases) while 58 (24%) were lesions-free (controls). The median duration of diabetes was 5 years in the control group vs. 4.5ys in the case group. The median age and BMI were similar in both groups. The percentage of male patients in the case group was more than in the control group (43% vs. 29% respectively). All demographic data are recorded and summarized in Table1.

Metformin usage in the study population

Patients without neoplastic lesions were more on Metformin as compared to controls (60% vs. 43%, P=0.02). There were no differences between single therapy with Metformin and combination therapy of Metformin and Insulin. Median duration of Metformin in patients without colorectal lesions was 2 years vs. 1 year in patients with colorectal neoplastic lesions (P=0.003, Table 2).

A multivariate logistic regression adjusted for age and gender demonstrated that overall Metformin was protective against colorectal lesions (OR=0.5, 95%CI: 0.2-0.9). This effect was restricted to patients who were on Metformin for more than 5 years (OR=0.2; 95% CI: 0.1-0.4), P=< 0.001) in contrast to patients on Insulin therapy (Table 3).

Table 1. Distribution of demographic variables by GI diagnosis.

	No GI disease N= 58	GI Disease N= 156	P value
Age, median (IQR) year	60 (54-64)	60 (55-68)	0.1
Male, no (%)	17 (29%)	67 (43%)	0.07
BMI, median (IQR)	32.9 (27.0-39.4)	32.0 (27.0-37.2)	0.1
Duration of diabetes, median (IQR) year	5 (4-7)	4.5 (4-6)	0.08
Smoking, no (%)	4 (7%)	13 (8%)	0.7
Alcohol, no (%)	4 (7%)	17 (11%)	0.4

Table 2. Distribution treatment variables by GI diagnosis.

	No GI disease	GI Disease	P value
Metformin, no (%)	35 (60)	67 (43)	0.026
• Single therapy, no (%)	14 (24)	25 (16)	0.2
• Combination therapy*, no (%)	21 (36)	42 (27)	0.2
Duration of metformin, median (IQR) year	2 (1-3)	1 (1-2)	0.003
Sulfonylurea, no (%)	13 (22)	36 (23)	0.9
Insulin, no (%)	37 (64)	84 (54)	0.2
Duration of insulin, median (IQR) year	2 (2-6)	2 (2-4)	0.4
Self-management, no (%)	4 (7)	13 (10)	0.5
TG, median (IQR)	116 (86-166)	106 (83-173)	0.8
LDL, median (IQR)	96 (77-142)	96 (74-157)	0.9
HDL, median (IQR)	42 (33-53)	51 (42-57)	0.015
* With insulin			

Table 3. Effect of metformin on GI lesion in multivariate logistic regression adjusted for age and gender.

	OR (95% CI)	P value
Overall	0.5 (0.2-0.9)	0.016
In patients with < 5 years diabetes N=96	1.7 (0.6-4.9)	0.3
In patients with ≥ 5 years diabetes N=117	0.2 (0.1-0.4)	<0.001

Table 4. Effect of insulin on GI lesion in multivariate logistic regression adjusted for age and gender.

	OR (95% CI)	P value
Overall	0.7 (0.4-1.4)	0.3
In patients with < 5 years Diabetes Mellitus	0.2 (0.1-0.8)	0.023
In patients with ≥ 5 years Diabetes Mellitus	1.5 (0.7-3.3)	0.3

Furthermore, Mu the age and gender adjusted multivariate logistic regression analysis demonstrated that patients with ≥ 5 years Diabetes Mellitus who are under treatment of Insulin had more chance to get colorectal cancer (OR=1.5 (0.7-3.3), however; in patients with <5 years Diabetes Mellitus, Insulin had protective effect. (OR=0.2 (0.1-0.8), P=0.023) (Table 4).

Discussion

Our study demonstrated that patients on Metformin had lower rate of colorectal neoplastic lesions. Our analysis showed an OR: 0.5 (95% CI:0.2-0.9) for patients taking Metformin compared to control group. However, there are numerous studies and mixed results on this field.

A systematic meta-analysis review and showed a 31% reduction in overall cancer with relative risk of 0.69 in patients taking Metformin compared with other antidiabetic drugs [12].

In 2014 a large case-control study was conducted to evaluate the effects of Metformin on the incidence of CRC in American population. In this study Metformin use appeared to be associated with a reduced risk of developing CRC among diabetic patients in the United States in 2014 [13]. Although, they found an indication of a protective effect of long-term metformin use against CRC in type II diabetics, however this effect was only seen in women. Regarding gender wise, an association between excess body weight and DM with an increased risk of colon cancer in males is demonstrated and supported [3].

On the other hand, in Germany, a recent retrospective study was done and they compared sulfonylurea and Insulin to Metformin regarding risk of cancer and found no reduced risk of cancer in Metformin users [14]. Another study was done in China and they assessed the risk of colorectal cancer with Metformin therapy in type 2 Diabetic patients. The analysis included five studies comprising 108,161 type 2 Diabetic patients. In this study, Metformin treatment was associated with a significantly lower risk of colorectal cancer (relative risk [RR]: 0.63 [95% CI 0.50-0.79]; *P*<0.001). After exclusion of one study that assessed colorectal adenoma, the remaining four studies included 107,961 diabetic patients and 589 incident colorectal cancer cases during follow-up. Metformin use was associated with a significantly lower risk of colorectal cancer (0.63 [0.47–0.84]; *P*=0.002). Finally, they concluded Metformin therapy appears to be associated with a significantly lower risk of colorectal cancer in patients with type 2 diabetes [15].

The mechanisms underlying this protective potential of Metformin

are not completely understood. The protective action of Metformin appears to be exerted by two main pathways. The first pathway involves reduction of endogenous systemic insulin levels, which may reduce insulin-stimulated cancer cell growth [16,17]. The second pathway relates to the activation of adenosine monophosphate-activated protein kinase (AMPK), which is recognized to inhibit cellular protein synthesis and growth. Particularly, Metformin was observed to activate AMPK and to have growth inhibitory actions on prostate and colon cancer cells, suggesting that this compound may be of particular value in attenuating the adverse effects of obesity on neoplasia [18,19].

Zaafar *et al.* [16] evaluated the role of Metformin in suppressing 1,2-dimethylhydrazine-induced colon cancer in diabetic and non-diabetic mice and found that Metformin down regulated tumor angiogenesis and augmented the antitumor effect of Oxaliplatin and protected against DMH-induced colon cancer in non-diabetic and diabetic mice [20]. Recent evidence for possible further mechanisms involving p53 on cyclin D1 has also been presented [21,22]. Whatever the precise mechanism, any reduction in the risk for cancer may be far-reaching, and this favorable effect adds to the clinical value of Metformin as the mainstay of antidiabetic treatment [23].

Although, there are some controversies about the efficacy of Metformin, however our study supports Metformin role in the prevention of colorectal cancer. More studies with large cohorts of Metformin, Insulin group and other oral antidiabetic drugs are needed to more accurately evaluate these relationships. The comparison of Metformin with other oral hypoglycemic drugs was not done in this study. In conclusion, patients on Metformin had lower rate of colorectal neoplastic lesions and as such Metformin might have a protective effect on these neoplastic lesions.

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