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Role of Metformin in the Management of Colorectal Cancer: A Systematic Review

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ABSTRACT

Colorectal cancer (CRC) is the second-leading cause of mortality and morbidity worldwide with multiple standard therapies that failed to improve outcomes. Metformin, an old, repurposed medication with pleiotropic effect in many cancers, arises as a possible treatment for CRC. This review aimed to assess the effect of metformin in addition to the treatment plan of CRC patients. To identify relevant studies, Google Scholar, PubMed, Egyptian Knowledge Bank (EKB), and clinical trial.gov were systematically searched. Pre-defined search keywords were used as "Metformin", "colorectal cancer", "randomized controlled trials", "interventional studies", and "observational studies". Only English-based trials that are in full text were included. A total of 19 studies with different therapeutic adjuvant treatment options were evaluated for metformin treatment effects in CRC. Randomized control trials and observational studies were the main interest of the review while preventive and pre-clinical studies including animals and cell lines were excluded. In conclusion, Most of the studies except a few showed promising results on overall survival (OS), disease-free survival, and relapse-free time for metformin use as treatment in CRC. Also, a reductive effect of metformin was shown in toxicities as oxaliplatin-induced peripheral neuropathy and poor prognostic features as vessel co-option vasculature in liver metastasis. Future clinical randomized controlled studies are essential to confirm these results.

Keywords: *Metformin; colorectal cancer; randomized controlled trials; interventional studies; observational studies.*

1. Introduction

Colorectal cancer is the third-leading type of cancer with a high incidence rate accounting for almost 1.9 million new cases every year. Not only that, it ranks as the second deadliest cancer type with almost 930,000 cases per year worldwide [1]. These high rates of CRC may be related to multiple factors including missed diagnosis, lack of early screening, and lifestyle habits [2].

Several risk factors are associated with the development of CRC. Lifestyle habits such as physical inactivity, obesity, westernized diet, alcohol intake, and smoking are the main stimulators for CRC initiation [3]. Moreover, hereditary genetic mutations in family members such as familial adenomatous polyposis (FAP) or

hereditary non-polyposis colorectal cancer (HNPCC) may induce gene alterations or inhibit repair systems that promote colorectal cell growth, the transformation of polyp into malignant cell and progression [4]. Also, long-standing colitis as in inflammatory bowel diseases; ulcerative colitis, and Crohn's disease, increases cell turnover and promotes CRC malignancy [5].

The complexity of CRC pathogenesis is the main factor for late diagnosis, as the time from induction of benign adenoma from hyperproliferative rapidly dividing cells till enlargement then transformation of adenoma to cancer via a series of alterations takes minimally from 10 up to 18 years [6]. Furthermly, in advanced stages of cancer, some of these cancerous adenomas may even spread via blood or lymphatic system to other parts of the body and metastasize [7]. The detection of such precarious development is laborious and requires early notification that can only be achieved through screening, especially in high-risk patients such as the elderly, patients with a family history, or comorbidities like diabetes. Frequently, non-invasive tools such as fecal occult blood test (FOBT) and fecal immuno-chemical test (FIT) are used to detect CRC presence. However, a confirmation of CRC pathological malignancy can only be achieved through invasive endoscopy with its different scopes [3, 8].

The management of CRC varies from surgery either curative or palliative, radiation, systematic chemotherapies, and immunotherapies to innovative targeted therapy. Early stages like stages 0-II, are generally treated with curative surgical resection, unlike late stages which require systemic therapy alongside surgery [9]. The choice of such therapies as systematic chemotherapies, immunotherapies, or targeted therapy is mainly based on the stage of CRC, resectability of cancer, and cost of therapy [10].

Multiple challenges are associated with immune and targeted therapies use, including high cost that isn't feasible for developing countries while systematic chemotherapies pose a high toxicity burden, increasing rates of resistance, and progressive treatment failure. Thus, a need for novel therapeutic options became an urgent necessity for CRC management [11].

Drug repurposing is one of the emerging strategies for developing new therapeutic options for an existing medication without the hassle of time consumption and cost wasting. These drugs not only offer known safety and tolerability but also may improve clinical outcomes and overcome resistance [12]. Metformin, a guanide derivative, originally used as a first-line anti-diabetic medication for type II diabetes mellitus, was found to have a pleiotropic effect in multiple comorbidities including cancer [13]. The anti-neoplastic effect of metformin is related to its induction and inhibition of diverse pathways. For instance, metformin's stimulatory effect on 5-adenosine monophosphate-activated protein kinase (AMPK), allows the regulation of the tumorigenesis process via inhibition of the mammalian target of rapamycin (mTOR). Also, metformin-AMPK activation leads to stimulation of liver kinase B1 (LKB1)/tuberin-sclerosis complex 2 (TSC2), which suppresses hyperproliferation of CRC cells [14]. Another pathway is the metformin inhibitory effect on insulin-like growth factor (IGF-1) which is majorly responsible for CRC initiation, progression, metastasis, and survival via proliferative downstream pathways as phosphatidylinositol 3 kinases (PI3K)/Akt/mTOR and RAS/RAF/mitogen [15, 16].

2. Material and methods

These systematic review findings were reported using the preferred reporting items for systematic review and meta-analysis (PRISMA) guidelines (http://www.prisma-statement.org).

2.1. Data sources and search strategy

A systemic search was conducted through three major electronic databases; Google Scholar (https://scholar.google.com/), PubMed (https://pubmed.ncbi.nlm.nih.gov/), and clinical trial.gov. (https://clinicaltrials.gov/). These electronic databases were accessed from the 3rd of September to the 5th of October 2023. Clinical trials till October 2023 were analyzed. Search terms used were "metformin treatment in colorectal cancer", "metformin and colorectal cancer: randomized controlled studies", "metformin treatment in colorectal observational studies ", and "metformin treatment and CRC".

2.2. Study screening and selection

Original English-written full-text trials were selected for inclusion in this review. Basic information such as the name of the main author, year of publication, study design, sample size, patient population, intervention, and control used, outcomes, and conclusions were reviewed for randomized control trials and observational studies used in this review.

2.3. Eligibility criteria

Inclusion criteria were randomized control trials (RCT), non-randomized clinical trials, and observational studies using metformin available in full-text version conducted on any stage of CRC. Preventive CRC studies, pre-clinical studies either in vitro or in vivo, and abstract-only clinical trials were excluded.

3. Results

The flow chart of study selection is demonstrated in **Fig. 1.** A total of 58761 studies were found during the investigational scholarly search. We eliminated 208 duplicate studies, 31,200 pre-clinical in vivo and in vitro studies, 27,200 preventive studies, 77 systematic review articles, and meta-analyses. The remaining qualified full text were 19 studies that evaluated the effect of metformin treatment in different stages of CRC.
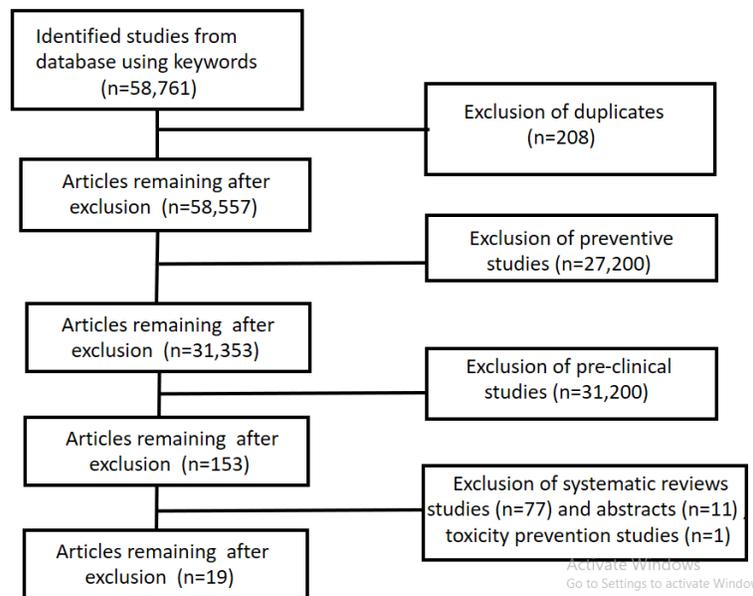

Fig. 1. The Flow chart of the study.

3.1. Overview of included studies

An overview of the included studies in this review based on trial design and study population is presented in **Table 1.** The sample size included in these studies ranged from 24 to 6222 patients and were all single-centered studies except one; the sub-TOSCA study. Three randomized control trials, 1 non-randomized clinical phase II Trial

and 17 observational cohort and retrospective studies were reviewed from different country regions including USA (n=6), Brazil (n=2), Egypt (n=1), Canada (n=1), Lithuania (n=1), China (n=1), Jordan (n=1), Ireland (n=1), Singapore (n=1), Italy (n=1), Denmark (n=1), Korea (n=1), France (n=1), UK (n=1), Turkey (n=1) and Taiwan (n=1).

Table 1: Summary of included studies.

Trial	Study design	Patient population	Intervention	Comparison	Outcome	Conclusion
Miranda et al (2016) [17]	Single arm	Refractory CRC patients (n= 50)	Metformin 850 mg twice daily was added after previous treatment with 5-FU, irinotecan, oxaliplatin, and Anti-EGFR	----------------	Effect on Disease Control Rate	Metformin + previous treatment showed a modest disease control rate with 22% of patients having tumor stabilization
Bragagnoli et al (2021) [18]	Single arm	Refractory CRC patients (n= 41)	Irinotecan + metformin 2500 mg orally	--------------	Effect on Disease Control Rate	Metformin + irinotecan demonstrated a good disease control rate of 41%
Akce et al (2023) [19]	Single arm	Refractory micro stable mCRC patients (n= 24)	Nivolumab + metformin 1000 mg orally	----------------	Effect on OS and PFS	No significant effect was found on either survival rate
Lee ,et al (2012) [20]	Cohort study	Stage II/III CRC patients (n= 344)	Metformin diabetic CRC users	Diabetic CRC non-metformin users	Effects on survival and relapse	Metformin improved overall survival (HR 0.18), time to recurrence (HR0.55), and relapse-free survival (HR 0.44)
Lee et al (2012) [21]	Cohort study	Stage III CRC patients (n= 595)	Metformin diabetic CRC users	Diabetic CRC non-metformin users	Effect on survival	Metformin use was associated with a decreased mortality rate (HR 0.66)
Garret et al (2012) [27]	Retrospective	Type II diabetic CRC patients (n= 424)	Metformin type II diabetic CRC users	Type II Diabetic CRC non-metformin users	Effect on overall survival	Metformin improved overall survival by 30%

Cossor et al (2013) [35]	Retrospective	Postmenopausal CRC patients (n= 2066),	Metformin diabetic CRC users	Diabetic CRC non-metformin users or non-diabetic	Effect on CRC-specific survival	No benefit was shown in the metformin group compared to other groups
Spillane et al (2013) [28]	Cohort study	Stage I-III CRC patients (n=207)	Metformin exposure	Other anti-diabetic rather than metformin exposure	Effect on CRC-specific survival mortality	Metformin use was associated with a significant reduction in CRC-specific mortality (HR 0.44)
Fransgaard et al (2015) [29]	Retrospective	Diabetic CRC patients (n= 1962) undergone surgery	Metformin diabetic colorectal cancer	Insulin/oral anti-diabetics diabetic colorectal	Effect on all-cause mortality	Metformin was found to increase survival by 15%
McMenamin, UC (2016)[25]	Retrospective	Diabetic CRC patients (n=1917)	Metformin diabetic CRC users	Other anti-diabetic medication in diabetic CRC users	Association between metformin and colorectal cancer-specific mortality	No association was found between metformin and cancer-specific mortality
Zhu et al (2017) [22]	Retrospective	Diabetic CRC patients (n= 585)	Metformin diabetic CRC users	Diabetic CRC non-metformin users	Association between metformin and survival in colorectal cancer	Metformin users had a better overall survival
Al Omari et al (2018) [31]	Retrospective	Diabetic CRC patients (n= 349)	Metformin diabetic CRC users	Other anti-diabetic medication in diabetic CRC users	Cancer risk and mortality reduction	Metformin users had better survival than other anti-diabetic medication (89 months vs. 36, respectively) and better progression-free survival (47 vs.21, respectively).
Dulskas et al (2019) [33]	Cohort study	Diabetic CRC patients (n= 1094)	Metformin diabetic CRC users	Diabetic CRC non-metformin users or non-diabetic	Effect on colorectal cancer-specific survival	Metformin users were found to have an improved OS in diabetic CRC (HR 0.91)
Vernieri et al (2019) [26]	Cohort study	High-risk stage II/III CRC patients (n= 120)	Metformin diabetic CRC users	Diabetic CRC non-metformin users	Effect on OS and relapse-free survival	No effect on OS or relapse-free survival was found in both groups
Xie et al (2020) [32]	Retrospective	Type II diabetic metastatic CRC patients (n= 282)	Metformin diabetic CRC users	Diabetic CRC non-metformin users	Effect on inhibition of metastasis	Metformin improved modestly the survival of only KRAS-mutated

						metastatic CRC
Kaltemeier et al (2021) [23]	Cohort study	CRC patients with liver metastasis that underwent hepatic resection (n= 270)	Metformin diabetic CRC users	CRC non-metformin users	Effect on OS and recurrence-free survival time	Metformin was shown to have longer OS (HR 0.6) (72 months vs.60 months) in non-metformin users, respectively. Also, metformin showed longer recurrence-free (HR 0.44) (49 months vs.33 months, respectively
Tahirini et al (2022) [30]	Retrospective	Diabetic CRC patients (n= 290)	Metformin diabetic CRC users	Diabetic CRC non-metformin users	Effect on OS and disease-free survival	Metformin users were associated with better OS (HR 0.45) and disease-free survival (HR 0.31)
Rada et al (2023) [34]	Retrospective	Diabetic CRC with liver metastasis (n= 108)	Metformin diabetic CRC users	Diabetic CRC non-metformin users or non-diabetic	effect on Poor Prognostic Vessel co-option Vasculature in liver metastasis and survival	metformin was shown to decrease the percentage of vessel co-option vasculature in liver metastasis thus better prognosis. and also had better survival than non-metformin users.
Chu et al (2023) [24]	Cohort study	Type II DM CRC patients that underwent surgery (n= 6222)	Metformin type II diabetic users	Non-metformin type II diabetic users	Effect of metformin on overall survival and association with risk of liver metastasis	Improvement was shown in metformin users group with HR 0.23 and an inverse association between metformin and risk of liver metastasis (HR 0.79)

CRC, Colorectal cancer; anti-EGFR, Anti-epidermal growth factor; mCRC, metastatic colorectal cancer; KRAS, Kristen rat sarcoma.

4. Discussion

Throughout the years, the effect of metformin and its possible beneficial anti-neoplastic effects when added to CRC treatment plan have been explored. A single-arm study by Miranda et al addressed the metformin effect on disease control rate in 50 refractory metastatic colorectal cancer (mCRC) patients previously treated with chemotherapy of 5-Fluorouracil,

irinotecan, oxaliplatin with anti-epidermal growth factor (EGFR) therapy where modest disease control rate was achieved [17]. Similarly, Bragagnoli et al single-arm study, reported a disease control rate when metformin was added to irinotecan therapy of 41 refractory mCRC patients [18]. On the contrary, Akce et al study on 24 refractory mCRC patients with microsatellite stability (MSS) showed no difference in OS and progression-free survival (PFS) when metformin and nivolumab were combined [19].

Since diabetes poses a high risk for CRC, most of the observational studies either cohorts or retrospective compared the effect of metformin in diabetic CRC patients that use metformin versus non-metformin users. For instance, the Lee et al. cohort study on 219 stage II/III diabetic CRC assessed the effect between metformin users and non-metformin users on OS, time to recurrence, and relapse-free time. The metformin users were found to have better OS with a hazard ratio (HR) of 0.18, better time to recurrence, and relapse-free time with HR of 0.55 and 0.44, respectively [20]. Also, Lee et al after a follow-up of 41 months for 595 stage III CRC patients, reported a decrease in mortality rate (HR 0.66) and percent mortality (27.5%) in the metformin user group versus (40.4%) in the non-metformin users. In addition, in specific CRC death, metformin users showed reduced rates of 21.3% vs. 30.9% in non-metformin users [21]. Moreover, the retrospective study on 585 CRC patients by Zhu et al reported an association between metformin use and better OS compared to non-metformin users [22]. Also, in the Kaltemeier et al cohort study, 270 CRC patients with liver metastasis who underwent hepatic resection were analyzed from January 2012 till December 2019 to determine the effect of metformin treatment on OS and recurrence-free survival. The patients on metformin showed longer OS in comparison to the non-metformin user group (72 months vs. 60 months, respectively) with an HR of 0.44. Also, a longer recurrence-free survival was reported in the metformin group (HR 0.44) at 49 months vs.33 months in the non-metformin users' group [23]. In addition, a retrospective study by Chu et al, conducted on 6222 type II diabetic CRC patients who underwent surgery from 2000 to 2012, assessed the effect of metformin on OS and liver metastasis risk. In this study, it was shown that metformin was able to improve the 5-year OS significantly following surgery (HR 0.33) in comparison to non-metformin users. Also, an inverse association between metformin and liver metastasis risk was found (HR 0.79) [24].

On the other hand, some studies reported non-significant differences in either cancer-specific mortality or OS or relapse-free survival with metformin use in comparison to non-metformin users. For instance, Mcmenamin U et al retrospective cohort study on 1917 diabetic CRC patients from 1998-2009 regarding cancer-specific mortality [25]. Also, a sub-study of TOSCA randomized control study by Vernieri et al on high-risk stage II/III CRC receiving fluoro-pyrimidine-based therapies showed no significant effect of metformin on OS (HR 1.51) or relapse-free survival (HR 1.56) compared to non-metformin users [26].

In type II diabetic patients, all studies analyzed the effect of metformin against other anti-diabetic medications. For instance, Garret et al assessed OS in type II diabetic CRC patients and reported an improvement in OS rate by 30% (56.9 months) versus (76.9 months) with other oral anti-diabetic medication users [27]. Also, a cohort study by Spillane et al in 207 stage I-III CRC patients reported an association between metformin exposure and reduction in CRC-specific mortality rate (HR 0.44) [28]. In Fransgaard et al study, they didn't only compare metformin users to other oral antidiabetic but also

to insulin in diabetic CRC that have undergone surgery in regards to overall mortality. After analysis, they revealed that metformin users were significantly different from the other two groups with a lower all-cause mortality rate of almost 15% [29]. Moreover, 290 patients were followed and analyzed for metformin effect on OS and disease-free survival by Tarhini et al. who reported metformin users to have better 2-year OS (HR 0.45) and disease-free survival (HR 0.31) in comparison to other antidiabetic users [30]. Also, Al Omari et al study, retrospective analysis on mortality reduction rate with metformin vs. other anti-diabetic medications in 349 diabetic CRC patients, showed a better survival rate in the metformin users with 49 months vs. 36 months in other group and an improved PFS (47 months vs. 21 months), respectively [31]. In addition, Xie et al study reported the analysis of 282 type II diabetic CRC patients with Kristen rat sarcoma (KRAS) wild and mutant type, metformin benefit was only shown exclusively in KRAS-mutated mCRC patients, unlike KRAS wild type patients where no improvement was shown [32].

Extensively, some studies analyzed metformin treatment in CRC patients in comparison to non-metformin users and non-diabetic patients. One of these studies is the Dulskas et al study that analyzed 1094 diabetic CRC patients from 2000 to 2012. The study compared the effect on OS where a significant difference was shown in the metformin group in comparison to other groups with HR of 0.91 [33]. Also, the Rada et al study in 108 liver mCRC patients has shown a decrease in mortality rates and better prognosis in the metformin group than in non-diabetic and other anti-diabetic medication users. They related such metformin benefits to the ability of metformin to decrease co-option vasculature in liver metastasis, a strong indicative of poor prognosis [34]. On the contrary, the observational study by Cossor et al analyzed 2066 post-menopausal diabetic CRC women for a median follow-up period of 4.1 years and showed no significant difference in CRC-specific survival in the metformin group in comparison to non-diabetics and other oral anti-diabetic medication groups [35].

Conclusion

Although studies about the effect of metformin treatment in CRC were controversial, the major sum of studies with their impactful data was indicative of the beneficial effect of metformin therapy as anti-neoplastic in CRC. Longer follow-up periods, more randomized control trials, and extensive subjects especially non-diabetic CRC are needed to further confirm the therapeutic effectiveness of metformin.

List of Abbreviations

CRC, Colorectal cancer;
EKB, Egyptian Knowledge Bank;
OS, Overall Survival;
FAP, Familial adenomatous polyposis;
HNPCC, Hereditary non-polyposis colorectal cancer;
FOBT, Fecal occult blood test;
FIT, Fecal immunochemical test;
AMPK, Adenosine monophosphate-activated protein kinase;
mTOR, mammalian target of rapamycin;
LKB1, Liver kinase B1;
TSC2, tuberin-sclerosis complex 2;
PI3K, Phosphatidylinositol 3 kinases;
RCT, Randomized control trials;
mCRC, Metastatic colorectal cancer;
Anti-EGFR, Anti-epidermal growth factor;
HR, Hazard ratio;
PFS, Progression-free survival;
KRAS, Kristen rat sarcoma.

Declarations

Consent to publish

All authors have read and agreed to the published version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Availability of data and material

All data generated or analyzed during this study are included in this published article in the main manuscript.

Competing interests

The authors have no financial or non-financial benefits to relate.

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