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Narrative review of the influence of diabetes mellitus and hyperglycemia on colorectal cancer risk and oncological outcomes

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ABSTRACT

Diabetes mellitus (DM) and hyperglycemia have been shown to have significant effects on the incidence, chemoresistance, and prognosis of colorectal cancer (CRC), as well as the outcomes of localized and metastatic CRC. Inflammation and endocrine effects may act as central mechanisms of DM and cancer and stimulate the insulin-like growth factor 1–phosphoinositide 3-kinase–Akt–mammalian target of rapamycin (IGF-1–PI3K–AKT–mTOR) pathway. Dysregulation of the AMP-activated protein kinase (AMPK) pathway leads to metabolic imbalance and indicates cancer risk. The use of metformin for chemoprevention has been shown to reduce CRC and adenoma incidence through the upregulation of AMPK, which causes cell cycle arrest in the Gap 1–S (G1–S) phase and inhibits the mTOR pathway, even potentially reversing the epithelial–mesenchymal transition. However, evidence of the effects of metformin remain controversial in cancer prognosis. Several genes, such as transcription factor 7-like 2*(TCF7L2),* tumor protein P53 inducible nuclear protein 1*(TP53INP1),* gremlin 1 *(GREM1)*, and potassium voltage-gated channel subfamily Q member 1*(KCNQ1),* are pleiotropically related to DM as well as cancer risk and prognosis. Epigenetic modification of members of the Let-7 family such as miR-497, miR-486, and miR-223 is strongly associated with impaired glucose tolerance and CRC risk. Herein we review the pathophysiological and epidemiological evidence as well as potential underlying molecular mechanisms by which DM and hyperglycemia affect CRC risk. We also suggest potential roles of glucose modulation in CRC therapy and propose an agenda for future research and clinical practice.

Abbreviations: DM, diabetes mellitus; CRC, colorectal cancer; HR, hazard ratios; ADA, American Diabetes Association; IGF, Insulin-Like Growth Factor; IGF1, Insulin-Like Growth Factor 1; PI3K, Phosphoinositide 3-kinases; AKT, RAC-alpha serine/threonine-protein kinase; mTOR, mammalian target of rapamycin; CENTRAL, Cochrane Central Register of Controlled Trials; FPG, fasting plasma glucose; 2-h PG, 2-h plasma glucose; OGTT, Oral Glucose Tolerance Test; HbA1c, Hemoglobin A1c; APC, Adenomatous polyposis coli; KRAS, Kirsten rat sarcoma viral oncogene homolog; TP53, tumor protein p53; CI, confidence interval; ERFC, Emerging Risk Factors Collaboration; NEJM, The New England Journal of Medicine; OS, overall survival; ROS, reactive oxygen species; PKC, protein kinase C; HBP, hexosamine biosynthetic pathway; AGEs, advanced glycation end-products; EMT, epithelial mesenchymal transition; BMJ, British Medical Journal; OR, odds ratio; I^2, I-square; RPG, random plasma glucose; BMI, Body mass index; AMPK, AMP-activated protein kinase; RAS, Rat sarcoma; GLUT1, glucose transporter 1; WNT, Wingless-related integration site; DKD, diabetic kidney disease; IGFBPs, insulin-like growth factor-binding protein; GWAS, Genome-wide association studies; WFS1, Wolframin ER Transmembrane Glycoprotein; PPARG, Peroxisome Proliferator Activated Receptor Gamma; HNF1B, Hepatocyte nuclear factor-1-beta; TCF7L2, Transcription Factor 7 Like 2; KCNQ1, Potassium Voltage-Gated Channel Subfamily Q Member 1; CAMK1D, Calcium/Calmodulin Dependent Protein Kinase ID; GREM1, Gremlin 1; TP53INP1, Tumor Protein P53 Inducible Nuclear Protein 1; IGF2BP2, Insulin Like Growth Factor 2 MRNA Binding Protein 2; TCF4, Transcription factor 4; VTI1A, Vesicle Transport Through Interaction With T-SNAREs 1A; DNA, deoxyribonucleic acid; 5-FU, 5-fluorouracil; STZ, streptozotocin; SEPT9, septin 9; VEGFR2, vascular endothelial growth factor 2; SMAD3, Mothers against decapentaplegic homolog 3; EHMT2, Euchromatic Histone Lysine Methyltransferase 2; FOLFOX, Folinic acid, Fluorouracil, Oxaliplatin; mCRC, metastatic colorectal cancer; PFS, Progression-free survival; U.S.FDA, United States Food and Drug administration; NIDDM, non-insulin-dependent diabetes mellitus; CSCs, cancer stem cells; ACF, aberrant crypt foci; ADM, antidiabetic medications; US, United States; RR, relative risk; pCR, pathologic complete response; TTR, the time to recurrence; RFS, recurrence-free survival.

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Introduction

The Global Burden of Disease project has reported that diabetes mellitus (DM) mortality across all ages increased by 34.7% from 2007 to 2017 [1], and deaths totaled 1.3698 million. Colorectal cancer (CRC) is the second leading cause of cancer deaths, accounting for 0.896 million deaths per year. CRC mortality across all ages increased by 27.8% between 2007 and 2017 [1]. In 1932, scientists assumed a causal effect between DM and cancer [2]. Current evidence suggests a pathophysiological association between DM and the incidence or prognosis of certain cancers [2]. Studies have reported a 30% increased risk for co-development of CRC in patients with DM [3,4]. According to a systematic review and meta-analysis, the overall hazard ratio (HR) of CRC incidence in patients with type II DM is 1.26, and the HR of CRC mortality in in patients with type II DM compared with patients without DM is 1.30 [5]. A umbrella review of 18 meta-analyses of observational studies by Tsilidis et al. identified correlations among DM and the risks of cholangiocarcinoma, breast cancer, and CRC [6]. The American Diabetes Association (ADA) guidelines acknowledge the positive correlation between DM and cancer risk. The biophysical characteristics of type II DM comprise insulin resistance, hyperglycemia, and inflammation. In general, hyperglycemia induces counterregulatory upregulation of insulin and insulin-like growth factor (IGF) levels, leading to cancer cell growth and proliferation [2]. Inflammation and endocrine effects may act as central mechanisms of DM and cancer and stimulate the IGF-1–phosphoinositide 3-kinase–Akt–mammalian target of rapamycin (IGF-1–PI3K–AKT–mTOR) pathway [7]. Exploring the pathophysiology and epidemiological factors of CRC and DM may advance the understanding of their linkages [8]. Several studies have reported an increased risk of cancer recurrence and mortality in patients with localized and regional CRC comorbid with DM [9]. A 2020 study asserted that DM has critical impacts on survival and disease progression in patients with advanced or metastatic CRC (mCRC) [3]. However, because of the possibility of selection bias or spurious observations in previous studies, the clinical importance of DM in mCRC remains unclear and controversial [3]. Moreover, the efficacy of DM medications such as metformin in reducing recurrence or improving survival in patients with resected CRC or mCRC has yet to be defined [7,10,11]. Herein we review the pathophysiological and epidemiological evidence and potential molecular mechanisms by which DM affects CRC risk. We also suggest potential applications of glucose modulation in CRC therapy and propose an agenda for future research and clinical practice.

Method

On September 14, 2020, we performed a search of the PubMed, Cochrane Review, Cochrane Central Register of Controlled Trials, and Clinical Trials.gov databases. Language and regional restrictions were not imposed. The search terms were as follows: “diabetes mellitus” AND “colorectal cancer” and “hyperglycemia” AND “colorectal cancer.” We conducted a thorough manual review of all bibliographies and relevant studies to identify additional potentially eligible studies.

Epidemiological association of DM, hyperglycemia, and CRC

DM and CRC

DM is a complex metabolic disorder characterized by chronic hyperglycemia and inflammation stemming from a consistent deficiency in insulin secretion or dysregulation of the insulin action pathway, which leads to dysfunction and failure of multiple organs. In type I DM, autoimmune-mediated destruction of endogenous pancreatic β-cells causes irreversible insulin deficiency and multiple immunological abnormalities. Type II DM, distinguished by insulin resistance, involves interactions between genetic, environmental, and behavioral risk factors. The 2020 criteria for DM diagnosis include the following: fasting plasma glucose (FPG) ≥ 126 mg/dL (7.0 mmol/L), 2-h plasma glucose (PG) ≥ 200 mg/dL (11.1 mmol/L) during oral glucose tolerance test (OGTT), and hemoglobin A1c (HbA1c) ≥ 6.5% (48 mmol/mol). DM is a risk factor for CRC as well as breast, lung, hepatic, pancreatic, uterine, and endometrial cancer [6] but is inversely associated with prostate cancer. DM may halt or slow prostate cancer development by reducing testosterone concentration, but the mechanism remains unclear. CRC is the second leading cause of cancer deaths and the fourth most commonly diagnosed cancer in the world [1]. In general, the *APC* gene first triggers the formation of colon adenomas, followed by mutations in *KRAS* or *TP53*. The progressive accumulation of multiple genetic and epigenetic mutations induces epithelial transformation and the subsequent development of adenocarcinoma. Individual characteristics such as following a Western dietary habit, having a history of obesity-related chronic conditions, and having inflammation of the microbiota are significantly associated with CRC.

In 1985, O’Mara et al. conducted a large multisite case–control study comprising 14,910 interviewees to examine the association between a prior diagnosis of DM and cancer incidence [12]. No significant associations were observed among male or female patients [4,12]. In 1998, Will et al. performed the first comparative study regarding DM and CRC [13], and they reported 1.30 (95% confidence interval [CI] = 1.03–1.65) as the CRC incidence density ratio in men with DM compared to men without DM. However, no significant results were noted between women with and without DM [13]. In 2009, the Emerging Risk Factors Collaboration (ERFC) began a serial analysis of the relationship of DM and other metabolic markers (including lipids and C-reactive protein) with vascular disease outcomes and cause-specific deaths [14]. Following the publication of a series of ERFC reports [14], Seshasai et al. performed a pooled analysis of 97 prospective studies and revealed that the HR between DM and CRC mortality was 1.40 (95% CI = 1.20–1.63) [15]. DM-related CRC incidence and mortality have been investigated in large case–control and cohort studies [13,16]; however, the evidence is inconsistent due to omitted variable bias [4]. An updated systematic review and meta-analysis of 24 studies published in 2012 [17] indicated that individuals with DM are much more likely to develop CRC (HR = 1.26, 95% CI = 1.20–1.31) than those without DM. In an updated meta-analysis of 29 cohort studies conducted in North America, Europe, and Asia, Wu et al. reported that the relative risk (RR) of CRC incidence in individuals with DM is 1.22 (95% CI = 1.19–1.26) [18]. The positive correlations remained significant even after sex was controlled for [18]. The ADA guidelines acknowledge the positive correlation between DM and cancer risk. A large-scale population-based analysis from Canada found that patients with CRC are 53% more likely to develop DM within a year of their CRC diagnosis (95% CI = 1.42–1.64). The risk within 5 years of diagnosis dropped to 19% (95% CI = 1.05–1.35) [19].

Mills et al. conducted a meta-analysis to examine primary outcomes in patients with CRC and diabetic status [20], and they reported an increased risk of all-cause mortality (RR = 1.17; 95% CI = 1.09–1.25) and cancer-specific mortality (RR = 1.12; 95% CI = 1.01–1.24) in patients with DM, respectively [20]. The patients with DM had worse disease-free survival (DFS) than those without DM. In 2017, Zhu et al. conducted a meta-analysis of 36 cohort studies comprising 2299,012 individuals in total, and the robustness and credibility of the results were confirmed through subgroup analysis [21]. Diabetic status was found to predominantly reduce overall survival (OS) in patients with CRC [21]. A population-based cohort study also indicated that diabetes promotes higher all-cause mortality in patients with CRC [22]. A 2020 large-scale updated meta-analysis by Becker et al. demonstrated that patients with CRC comorbid with DM have worse all-cause mortality and DFS outcomes [23].

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Hyperglycemia and CRC

According to the 2020 ADA guidelines, hospitalized patients are considered to have hyperglycemia when their blood glucose levels exceed 140 mg/dL (7.8 mmol/L). Chronic hyperglycemia initially induces cell proliferation and DNA damage through the generation of reactive oxygen species (ROS). ROS mediate the subsequent activation of protein kinase C and the hexosamine biosynthetic pathway (HBP) as well as the formation of advanced glycation end-products and the induction of the epithelial–mesenchymal transition (EMT). The expression of HBP, which promotes immune evasion and tumor metastasis by upregulating O-GlcNAcylation in tumor-associated macrophages, is strongly augmented by hyperglycemia. In addition, the level of inflammation-related markers such as tumor necrosis factor α (TNFα) promotes a tumor-favorable microenvironment. The induction of inflammatory response and apoptotic changes when having hyperglycemic status has been verified by *in vitro* and *in vivo* studies.[9] In 1956, Warburg posited that elevated blood glucose stimulates carcinogenesis, since then, several theories regarding the promotional effect of hyperglycemia on the prevalence or mortality of malignancies have been proposed. A large population-based prospective cohort study of more than 140,000 Austrian adults published in 2006 [24] indicated that fasting hyperglycemia (6.1–6.9 or ≥7.0 mmol/L) contributed to higher incidences of non-Hodgkin's lymphoma in men and CRC or bladder cancer in women [24]. Xu et al. performed a meta-analysis involving 25,566 patients and 5706,361 patients to identify the role of high fasting glucose levels and other glucose metabolism markers in CRC [25]. The pooled overall risk of fasting glucose level was 1.12 (95% CI = 1.06–1.18), and fasting levels of insulin and HbA1c were also significantly positively correlated with cancer risk. Another study reported that the RR of CRC for each 20 mg/dL incremental increase over the FPG baseline was 1.015 (95% CI = 1.012–1.019) [26]. In a prospective study, Pang et al. followed approximately 0.512 million Chinese participants between 2004 from 2008 for 10 years, and they found a relatively high random plasma glucose (RPG) was strongly associated with CRC. A 4% increased risk of CRC incidence (95% CI = 1.02–1.05) and mortality (95% CI = 1.01–1.07) was evident for each 1 mmol/L incremental increase over baseline RPG [27]. Overall, the evidence suggests that early detection of hyperglycemia might assist in preventing the co-development of CRC in patients with DM.

Epidemiology of CRC risk: global patterns and regional differences

According to the Global Cancer Statistics 2018, CRC incidence is generally three times higher in countries with transition economies, such as those in Europe, Australia, New Zealand, North America, and East Asia, than in transitioning economies. The overall prevalence is higher in Western than in Asian countries [28]. However, CRC incidence has gradually escalated in Asia-Pacific populations in the past several decades, especially in East Asian nations, such as Japan and South Korea [28]. Conversely, the CRC incidence rate in Africa and in South Asia is generally low [28]. This is attributable to multifactorial influences such as dietary patterns, smoking, alcohol consumption, obesity, following of a Western lifestyle, and microbiome conditions [2,29,30]. The consumption of a Western diet, characterized by high fat and low fiber, can lead to insulin resistance and hyperinsulinemia, stimulating the growth of colorectal tumors [16]. In addition, long-term cigarette smoking increases CRC mortality because nicotine enhances the growth and migration of colon cancer cells [2].

Regarding the role of microbiology in CRC oncogenesis, the pathophysiological interaction between intestinal microbiota and the immune system can be understood by referring to Molecular Pathology and Epidemiology (MPE) studies [31,32]. Gut microbiota can mediate the modulation of metabolites and genotoxins by developing as opportunistic microorganisms in a tumor-immune microenvironment [33]. Studies have demonstrated associations among *Fusobacterium nucleatum,* CRC, and the serrated neoplasia pathway that can result in poor prognosis [31,32]. Studies have also indicated that *Fusobacterium nucleatum* can mediate tumor response to immunotherapy and chemotherapy [31,32]. The abundance of certain gut microbiota is determined by the host's genes. In one study, the family *Christensenellaceae* was the most highly heritable taxon among the available dataset and directly determined the phenotype of the host [34]. Members of a family are more likely to share similarities in microbiota among each other than among unrelated individuals. This can be attributed to shared environmental influences, such as dietary and lifestyle preferences [34]. Recent studies have indicated that metformin regulates the abundance of gut microbiota and inhibits CRC carcinogenesis in patients with DM [33]. In addition, the bidirectional relationship between colon epithelial cells and microbiota may increase the susceptibility to CRC and metabolic diseases, especially obesity [8].

Obesity mediates the predominant risk for DM and cancer. Pearson-Stuttard et al. estimated that 5.7% of all incident cancers are caused by the interaction of DM and a high body mass index (BMI) [35]. The impact of a high BMI on cancer prevalence from 1980 to 2002 was two times higher than that of DM [35]. Approximately 3.6% of all new cancer cases in 2012 were related to excessive BMI, especially CRC in men and postmenopausal breast cancer in women [29]. A series of MPE investigations revealed that FASN(fatty acid synthase) expression, STMN1 expression, CDKN1A (p21) expression, and CDKN1B (p27) cellular localization were linked to energy balance, which influences tumor cell behavior and tumor–host interactions [32].

Populations in India, China, Indonesia, Mexico, and the United States account for the majority of diabetes-induced deaths [1,36]. The global prevalence of type II diabetes in men is 13.2% higher than that in women [36], and the greatest sex disparities are found in high-income countries in Asia-Pacific and Central Europe. Men constitute the majority of CRC diagnoses, particularly in South Korea, Japan, China, and Hong Kong. A prospective cohort study comprising 408,931 South Koreans indicated that obesity and poor metabolic health led to greater CRC risk and that this trend was more evident in men than in women [37]. This phenomenon may be induced by the dysregulation of several mediating hormones, such as the levels of estradiol, sex hormone–binding globulin, and adiponectin are lower in men than in women.

A study of 953,382 enrollees of a national DM registry reported that women with type I DM had significantly higher risks of CRC than did men with type I DM. However, the CRC incidence ratios for men and women with type II DM were comparable [38]. A 12-year prospective study that followed the profiles of 75,219 patients enrolled in the Norwegian Cancer Registry indicated that women with DM were 55% more likely to develop CRC than women without DM (95% CI = 1.04–2.31) [16]. No significant differences were noted for men [16]. Cancer incidence was higher in women under hyperglycemic status with FPG concentrations over 8.0 mmol (RR = 1.98, 95% CI = 1.31–2.98) [16]. The Netherlands Cohort Study on Diet and Cancer reported an 80% higher risk of proximal colon cancer in women with DM (95% CI = 1.10–2.94) [39]. In an analysis of two large prospective cohorts in the United States, Ma et al. noted that under type II DM was closely associated with the development of CRC in men but not in women [40]. Because of the inconsistencies in the evidence linking sex to CRC risk, this issue should be approached with caution.

A Mendelian randomization study by Goto et al. explored correlations between DM and cancer risk in the Japanese population [41]. The evidence was insufficient to support prominent associations between genetically predicted DM and CRC. Elucidating the epidemiology of CRC risk in global patterns and regional differences may aid in the establishment of a framework for public health interventions [8,42]. Table 1 summarizes the epidemiological association between DM and CRC risk, and Table 2 displays the effects of DM on CRC prognosis.

Pathophysiology of DM and hyperglycemia in CRC

Potential underlying molecular mechanism of cancer risk in DM and hyperglycemia

In the pathogenesis of tumors and other malignancies, aerobic glycolysis is enhanced through the increase of glucose transportation into

Table 1
Impact of DM on CRC incidence.

Reference	Type	Area	No. of case	Risk for colorectal cancer (95% CI)
Will et al. [13]	Cohort	U.S.	3218	HR= 1.30 (1.03–1.65) for men, p <0.05 HR= 1.16 (0.87–1.53) for women, no significance
Yang et al. [84]	Case-control	U.K.	10,447	OR= 1.42 (1.25–1.62) OR= 1.36 (1.16– 1.61) for men OR= 1.38 (1.14–1.67) for women
Deng et al. [17]	Meta-analysis	U.S. Europe	38,182	RR= 1.26 (1.20–1.31) and Asia $P_{heterogeneity}$ = 0.296
Tsilidis et al. [6]	Meta-analysis	Worldwide	61,490	RR= 1.27 (1.21–1.34)
Harding et al. [38]	Cohort	Australia	10,848	SIR= 1.18 (1.15–1.21) for men SIR= 1.16 (1.13–1.20) for women
Singh et al. [19]	Cohort	Canada	39,707	HR = 1.53(1.42- 1.64) in the 1st year postdiagnosis HR = 1.19(1.05- 1.35) in the 5th year postdiagnosis
Shin et al. [37]	Cohort	Korea	5108	aHR = 1.216 (1.112–1.329)
de Kort et al. [39]	Cohort	Netherland	3056	HR of overall CRC = 0.95 (0.75–1.20) for men 1.08 (0.85–1.37) for women HR of proximal CC = 1.44 (1.05–1.99) for women
Ma et al. [40]	Cohort	U.S.	3000	HR= 1.42 (1.12–1.81) for men HR= 1.17(0.98–1.39) for women
Goto et al.[41]	Mendelian Randomization	Japan	10,447	HR= 0.90 (0.74–1.10)

U.S., United States; U.K., United Kingdom; CRC, colorectal cancer; HR, hazard ratio; OR, odds ratio; RR, relative risk; SIR, standardized incidence ratio; aHR, adjusted hazard ratio; CC, colon cancer.

Table 2
Impact of DM on CRC prognosis.

Reference	Type	Area	No. of case	CRC prognosis (95% CI)
Seshasai et al. [15]	Pooled	Worldwide	3876	Colorectal mortality: analysis HR=1.40 (1.20–1.63)
Tsilidis et al. [6]	Meta-analysis	Worldwide	4394	Colorectal mortality: RR= 1.20 (1.03–1.40)
Mills et al. [20]	Meta-analysis	China, U.S, Taiwan and Europe	1853	All-cause mortality: RR = 1.17 (1.09–1.25) Cancer-specific mortality: RR = 1.12(1.01–1.24) Disease-free survival: RR = 1.54 (1.08–2.18)
Zhu et al. [21]	Meta-analysis	U.S., Europe, Asia and Oceania	N/A	Overall survival: HR=1.18(1.12–1.24)
Qiang et al. [22]	Cohort	Canada	44,178	All-cause mortality: HR= 1.08 (1.04- 1.12) Cancer-specific survival: HR= 1.0 (0.95- 1.06)
Becker et al. [23]	Cohort	U.S., Europe Taiwan, Korea And other Asia Countries	over 240,000 partcipants	All-cause mortality: RR = 1.17 (1.09–1.25) Cancer-specific mortality: RR = 1.12(1.01–1.24) Disease-free survival: RR = 1.54 (1.08–2.18)

U.S., United States; CRC, colorectal cancer; HR, hazard ratio; RR, relative risk.

the cytoplasm to support cell proliferation. The Warburg effect is present in malignant cells regardless of the presence of well-functioning mitochondria. Glucose metabolism is mainly mediated through insulin receptor signaling in the AMP-activated protein kinase (AMPK) signaling pathway [43]. Subsequent activation and overexpression of *RAS, PI3K/AKT, c-Myc*, and glucose transporter 1 (*GLUT1*) facilitate glucose influx [43]. Dysregulation of the AMPK pathway typically leads to metabolic imbalance. This occurs in major chronic conditions, such as obesity, inflammation, atherosclerosis, DM, and cancer. The upregulation of GLUT1 facilitates glucose uptake by cancer cells, which is regarded as a predictor of poor CRC prognosis. Type I DM is characterized by insulin deficiency rather than insulin resistance; therefore, fewer epidemiological studies have identified supporting evidence for the interaction between type I DM and cancer risk [2]. By contrast, type II DM is distinguished by insulin resistance, hyperglycemia, and inflammation. Chronic hyperglycemia induces counterregulatory upregulation of insulin and IGF levels [2] and further stimulates the IGF-1–PI3K–AKT–mTOR pathway [7]. Because the insulin receptor is widely expressed in CRC cells, tumor cell bioenergetic requirements are partially fulfilled by high plasma glucose levels through the successive induction of the EMT, insulin/IGF-1, and PI3K–AKT–mTOR signaling. Elevated IGF may induce *VEGF* gene transcription, which promotes angiogenesis and further tumor invasion. Wnt/β-catenin signaling also cross-interacts with insulin-stimulated proto-oncogene expression, mediating complications of DM such as diabetic kidney disease (DKD). IGF-1 modulates mitogenic antiapoptotic functions and hormone effects by binding

IGF-binding proteins (IGFBPs). In a systematic review and multivariate meta-regression analysis of the interaction between IGF-1 and cancer risk by Renehan et al., high levels of IGF-1 and IGFBP-3 were significantly associated with a 49% increased risk of prostate cancer (95% CI = 1.14–1.95) and a 65% increased risk of premenopausal breast cancer (95% CI = 1.26–2.08) [44], but no significant associations were observed in CRC (OR = 0. 77, 95% CI = 0.36–1.66) [44]. A serologic and Mendelian randomization analysis by Murphy et al. indicated that alterations in circulating IGF1 affected CRC development (HR = 1.11, 95% CI = 1.05–1.17) [45]. To date, this is the largest and most comprehensive investigation to validate the association between type II DM, insulin resistance, and CRC [45].

Gene interactions between DM and CRC

Genome-wide association studies [46,47] have identified gene variants related to increased risk of type II DM, including Wolframin ER transmembrane glycoprotein *(WFS1)*, peroxisome proliferator activated receptor gamma *(PPARG)*, hepatocyte nuclear factor-1-beta (*HNF1B*), transcription factor 7-like 2 (*TCF7L2*), potassium voltage-gated channel subfamily Q member 1 (*KCNQ1*), calcium-/calmodulin-dependent protein kinase ID, gremlin 1 (*GREM1*), tumor protein P53 inducible nuclear protein 1 (*TP53INP1*), *ATP5G1*, and IGF-2 mRNA-binding protein 2 (*IGF2BP2*), all of which have effects on insulin secretion. Moreover, their dysregulation may lead to the development of type II DM. *TCF7L2, TP53INP1, GREM1*, and *KCNQ1* are pleiotropically related to cancer risk and CRC prognosis [8,48–53]. These susceptibility loci also influenced energy balance, inflammation, and one-carbon metabolism [32]. *TCF7L2* is the most critical locus and is associated with type 2 DM risk [46,47,54], and is also the most common gene mutation in CRC in East Asian populations [48]. *TCF7L2* typically suppresses tumor invasion, but its mutation increases malignancy and enhances cell invasion [48]. *TCF7L2* encodes transcription factor 4 *(TCF4)* and activates the WNT/β-catenin-signaling pathway, inducing the expression of *cyclin D1* and *c-Myc* in CRC pathogenesis [49,51]. Recurrent *VTI1A-TCF7L2* gene fusion is commonly observed in CRC [54]. In addition, deficient *TP53INP1* mediation leads to tumorigenesis. In CRC, miR-221 downregulates TP53INP1 expression and inhibits autophagy [50]. Overexpression of the *GREM1* gene in stage II CRC is correlated with poor prognosis [52]. In a study on the Chinese population, Li et al. postulated that *GREM1* contributes to CRC susceptibility by disrupting a hsa-miR-185–3p binding site [53]. GREM1 expression in CRC is also promoted by the interaction of TCF7L2 complexes and β-catenin [8]. Pursuing further clinical evidence is warranted to support these findings.

Epigenetic modification in CRC and DM

DNA methylation results in the amplification of oncogenes and the inactivation of tumor suppressor genes, inducing malignancy by disrupting the stability of proliferation and apoptosis. In the mammalian genome, local DNA sequence context may influence the assembly of a methylation reaction, and germline variations in putative cis-acting elements may mediate epigenetic regulatory mechanisms [32]. Aberrant hypermethylation and hypomethylation may coexist. In CRC, hypomethylation status provides more potential for the development of invasion in advanced tumors than does hypermethylation. *Septin 9* (*SEPT9*) methylation is highly sensitive and specific in identifying CRC. Church et al. observed a positive correlation between *SEPT9* methylation sensitivity and CRC stage [55]. They indicated that the sensitivity of *SEPT9* in stage IV CRC patients was as high as 77.4%, whereas that for advanced adenoma was only 11.2% [55]. Aberrantly methylated genes in type II DM islets cause β-cell dysfunction, subsequently leading to impaired glucose tolerance and DM. In type II DM, DNA hypermethylation of the promoters of *SEPT9, Cdkn1a*, and *Pde7b* increases gene expression in type II DM islets, impairing clonal β-cell function and reducing glucose-stimulated insulin secretion [56]. Overexpression of *SEPT9* significantly improves cellular glucagon expression. In 2004, Poy et al. first demonstrated that miR-375 has the ability to suppress glucose-induced insulin secretion and exocytosis by targeting myotrophin [57]. The upregulation of miR-21 restricts hepatic gluconeogenesis, thereby alleviating glucose and insulin intolerance. In diabetic nephropathy, miR-21 overexpression exerts the opposite effect and increases the risk of transforming growth factor beta 1–mediated fibrosis [58]. Among these epigenetic modifications, *SEPT9*, miR-16, and miR-21 are implicated in CRC, DM, and DKD [58]. As for miR-16, it was shown to mediate cell cycle arrest, inhibits tumor cell growth, and enhances sensitivity to chemotherapy [59]. On the basis of a meta-analysis of studies investigating correlations between DM and CRC, a study indicated that CRC recurrence was less likely in patients with blood glucose concentrations under 110 mg/dL [60]. Previously, our team posit that hyperglycemia considerably affects CRC prognosis by downregulating miR-16, which occurs through the targeting of *Myb* and *VEGFR2* [60].

A 2019 study by Chen et al. listed several miRNAs and long noncoding RNAs that regulate the IGF-1 receptor in DM and cancer [61], including the Let-7 family, chiefly miR-497, miR486, and miR-223. Downregulation of the Let-7 family may improve glucose tolerance through activation of the Akt–mTOR pathway. In colon and prostate cancer, the Let-7 family suppresses the overexpression of the IGF-1 receptor and then inhibits carcinogenesis [61]. At high blood glucose levels, miR-497 enhances insulin secretion, and it might play various roles in cancer and chemosensitivity [61]. In the Asian population, miR-486 negatively predicts impaired glucose tolerance, and it is often downregulated in lung and hepatic cancer [61]. Regarding miR-223, it mediates glucose intake and improves insulin resistance and is typically overexpressed in patients with type II DM. It is also upregulated in CRC through an inflammatory feedback loop, suppressing neoplastic proliferation [61].

Association between DM, hyperglycemia, and chemoresistance

Diabetes acts as a prognostic factor in the pathogenesis and recurrence of certain cancers. Hyperglycemia enhances CRC chemoresistance to 5-fluorouracil (5-FU), fluoropyrimidine, oxaliplatin, and irinotecan therapies [3,43]. Ikemura and Hashida reported that the therapeutic efficacy of oxaliplatin and fluorouracil was limited in hyperglycemic mice treated with streptozotocin, and their OS was also affected by chemoresistance [62]. Uncontrolled blood glucose indicates high risk of severe 5-FU cytotoxicity and CRC chemoresistance. Our previous study demonstrated that high glucose (15 mM) attenuates the growth inhibition of 5-FU and reduces apoptosis by increasing DNA replication [43]. A series of studies from our team published since 2008 [60,63,64] has suggested an association between high glucose concentration and CRC pathogenesis. In a study of 157 patients with stage III CRC in hypoglycemic and hyperglycemic status (glucose concentration ≥126 or <126 mg/dL, respectively) [63], we found that hyperglycemia reduced the therapeutic efficacy of oxaliplatin therapy. As verified through multiple biochemical experiments, hyperglycemia may affect cancer prognosis in DFS and OS through the phosphorylation of SMAD3 and Myc and the upregulation of EHMT2 [63]. This finding is consistent with those of previous studies [64]. After metformin administration, the increase in pSMAD3 and pMyc levels ascribable to hyperglycemia was reversed [63].

As mentioned, insulin receptor signaling and the AMPK signaling pathway mediate glucose metabolism. The other main regulator of mitochondrial biogenesis is peroxisome proliferator–activated receptor gamma coactivator 1-alpha (PGC-1α), the phosphorylation and expression of which AMPK can stimulate. Specifically, PGC-1α regulates gene expression in mitochondrial biogenesis and reduces ROS synthesis through mitochondrial oxidative phosphorylation. Studies have indicated the contribution of mitochondrial dysfunction to chemoresistance [65]. Combined with our unpublished results, we postulate that hyperglycemia may be associated with serial cross-interaction with PGC-1α,

Table 3
Impact of metformin treatment on CRC incidence.

Reference	Type	Area	No. of case	Risk for colorectal cancer (95% CI)
Singh et al. [72]	Meta-analysis	U.S., Asia and Europe	13,871	OR= 0.89 (0.81–0.99)
Sehdev et al. [73]	Case-control	U.S.	2682	AOR= 0.88 (0.77–1.00), $p = 0.05$
Higurashi et al. [74]	Clinical trial	Japan	71	RR=0.60 (0.39–0.92), $p = 0.016$ on prevalence of adenoma RR=0.67(0.47–0.97), $p = 0.034$ on prevalence of total polyps
Dabrowski et al. [75]	Case-control	Poland	203	OR=0.310 (0.183–0.525), $p<0.001$
Chang et al. [64]	Cohort	Taiwan	19,082	Intensity of metformin use (DDD/month) Never use: HR= 0.73(0.61–0.86), $p<0.001$ ≤10 g: HR= 0.24(0.17–0.33), $p<0.001$ 10–20 g: HR= 0.14(0.08- 0.24), $p<0.001$
Demb et al. [77]	Case-control	U.S.	2620	OR=0.92(0.87–0.96)
Yang et al. [78]	Meta-analysis	U.S., U.K., and Taiwan	N/A	RR = 0.884 (0.829–0.943)
Ng et al. [79]	Meta-analysis	Worldwide	N/A	RR= 0.77(0.67- 0.88), $p < 0.001$ on colorectal adenoma RR= 0.61(0.42- 0.88), $p = 0.008$ on advanced adenoma RR= 0.76(0.69–0.84), $p < 0.001$ on CRC
Dulskas et al. [76]	Cohort	Lithuanian	1213	SIR=1.47 (1.36–1.58) for metformin user SIR=2.14 (1.95- 2.35) for non-metformin user

U.S., United States; U.K., United Kingdom; CRC, colorectal cancer; HR, hazard ratio; OR, odds ratio; RR, relative risk; SIR, standardized incidence ratio; AOR, adjusted odd ratio; DDD, defined daily dose.

enhancing chemoresistance in patients with CRC. The field of hyperglycemia research has great potential for development.

Association between DM and clinical outcomes of mCRC under chemotherapy treatment

Studies have demonstrated associations between DM and recurrence and mortality in localized or regional CRC [9,20]. However, the evidence on advanced or metastatic CRC remains conflicting [3,10,66]. As mentioned, hyperglycemic status affects sensitivity to chemotherapy through multiple regulatory routes. Individuals with DM or hyperglycemic status may have higher risks of tumor progression or chemotherapy-related adverse events compared with those without DM. Ramanathan et al. conducted a retrospective study of the effect of DM on the incidence and severity of peripheral sensory neuropathy in patients with CRC receiving oxaliplatin therapy, but the results were nonsignificant [66]. In 2019, a pooled analysis of two phase III studies (756 patients) on the impacts of DM on the efficacy of the first-line chemotherapy regimen FOLFOX and related complications and adverse events was conducted [10]. OS, progression-free survival (PFS), and the severity of oxaliplatin-induced paresthesia did not differ significantly between the DM and non-DM groups [10]. The information provided by this clinical trial was more credible and of higher quality than population-based studies [10]. Bano et al. concluded that peripheral neuropathy was not significantly associated with FOLFOX therapy in groups of patients with mCRC regardless of whether DM was a comorbidity. A prospective study by Brown et al. evaluated 2326 patients with mCRC receiving first-line chemotherapy and bevacizumab or cetuximab. Associations between DM and patient outcomes were examined [3], and PFS was worse in the DM group (HR = 1.16, 95% CI = 1.03–1.30) [3]. The OS in the groups with and without DM was 22.7 and 27.1 months, respectively (HR = 1.27, 95% CI = 1.13–1.44) [3]. In essence, risks of mortality and tumor progression were higher in patients with mCRC comorbid with diabetes. Regardless, the impact of DM on chemotherapy-related complications remains unclear.

Therapeutic implications

Antineoplastic role of metformin on CRC risk

Table 3 summarizes the results of epidemiological studies on metformin and CRC. Metformin is an oral biguanide agent approved by the United States Food and Drug Administration in December 1994 [67]. It is recommended as a first-line therapeutic for type II DM. Metformin suppresses hepatic gluconeogenesis and improves skeletal muscle glucose uptake by upregulating AMPK. AMPK caused G1–S-phase cell cycle arrest by inhibiting the mTOR pathway, suggesting that metformin may act as an antineoplastic agent. Hirsch et al. first demonstrated that metformin inhibits the growth of cancer stem cells in preclinical breast cancer models [68]. Epidemiological studies have supported the premise that metformin may play an antineoplastic role on the risk and progression of gastric cancer, lung carcinoma, ovarian cancer, pancreatic cancer, and head and neck carcinoma, among others [67]. It also has potential in the resensitization of treatment-resistant breast cancer [69]. Similar to findings from murine models, the first clinical trial on metformin observed that it inhibited the proliferation of colorectal aberrant crypt foci [70], which indicates its chemopreventive efficacy. A prospective, randomized controlled trial comparing metformin and placebo treatments confirmed the chemopreventive effects of low-dose metformin on the formation of metachronous colorectal adenoma [71].

In a meta-analysis by Singh et al. on associations between antidiabetic agents and CRC risk, CRC risk was 11% lower in the metformin group (OR = 0.89, 95% CI = 0.81–0.99) [72]. Conversely, higher CRC risk was noted in the insulin group (OR = 1.11, 95% CI = 0.97–1.26). In a case–control study of the US population, Sehdev et al. performed serial adjustment of confounding factors and found that CRC incidence decreased by 12% following metformin treatment (95% CI = 0.77–1.00) [73]. In a randomized phase III clinical trial comprising 151 partici-

Table 4A
Studies reporting favorable outcomes of metformin treatment on CRC.

Reference	Type	Area	No. of case	CRC prognosis (95% CI)
Spillane et al. [80]	Cohort	Ireland	207	Cancer-specific mortality: HR= 0.44 (0.20–0.95) for high-intensity metformin user
Meng et al. [81]	Meta-analysis	Ireland, U.S, Korea and Europe	4060	Overall survival: HR = 0.75 (0.65- 0.87) CRC-specific survival: HR= 0.79 (0.58–1.08)
Ng et al. [79]	Meta-analysis	Worldwide	N/A	Overall survival on CRC: HR= 0.6(0.53–0.67), $p < 0.001$ CRC-specific survival: HR= 0.66(0.59–0.74), $p < 0.001$ Overall survival on mCRC: HR= 0.77 (0.68–0.87), $p< 0.001$
Yu et al. [33]	Umbrella review	Worldwide	N/A	Metformin use and colorectal cancer OS was supported by highly suggestive evidence. ($P < 10^{-6}$, >1000 cases, $P < 0.05$ of the largest component study in the meta-analysis)

Table 4B.
Metformin administration with favorable CRC outcomes.

Reference	Type	Area	No. of case	CRC prognosis (95% CI)
Singh et al. [11]	Clinical trial	U.S.	267	Disease-free survival: aHR= 0.90 (0.59–1.35), $p = 0.60$ Overall survival: aHR= 0.99 (0.65–1.49), $p = 0.95$ The time to recurrence: aHR= 0.87 (0.56–1.35), $p = 0.53$
Fransgaard et al. [82]	Cohort	Denmark	966	Disease-free survival: HR= 1.06 (0.87–1.15), $p = 0.57$ Recurrence-free survival: HR= 1.01 (0.89–1.15), $p = 0.85$ All-cause mortality: HR = 1.07 (0.94–1.22), $p = 0.33$
Vernieri et al. [7]	Clinical trial	Italy	76	Overall survival: aHR=1.51(0.48–4.77), $p = 0.4781$ Recurrence-free survival HR=1.56 (0.69–3.54), $p = 0.2881$

U.S., United States; CRC, colorectal cancer; HR, hazard ratio; OR, odds ratio; aHR, adjusted hazard ratio.

pants, Higurashi et al. found that low-dose metformin exerted chemopreventive effects after polypectomy in patients without DM [74]. Other case–control and cohort studies from various countries such as Lithuania, Poland, and the United States [75–77] have reported similar findings, confirming that metformin confers benefits on colorectal adenoma and CRC in patients with type II DM. In another study, the antineoplastic role of metformin was verified [78]. A 2020 meta-analysis of 58 studies and 1733,229 patients reported that metformin treatment not only reduced CRC incidence and prevented recurrence but improved OS and CRC-specific survival, especially OS in the mCRC group (HR = 0.77, 95% CI = 0.68–0.87) [79].

In our nationwide cohort study [64], we found that high-dose metformin treatment reduced the risk of CRC development in the Taiwanese population [64]. The HR of cancer incidence decreased by 14%–73% (depending on duration of use) [64], indicating that high-dose metformin had chemopreventive effects. However, patient compliance and medication adherence may affect the therapeutic efficacy of long-term metformin treatment.

Metformin as an auxiliary agent in improving cancer prognosis or the efficacy of chemotherapy or radiotherapy

Epidemiological studies have provided evidence in support of the premise that metformin improves cancer prognosis and survival (Table 4A). Metformin enhanced response to radiotherapy and chemotherapy through synergistic interactions, indicating that it may help induce tumor regression. In a cohort study of metformin exposure and survival in older Irish adults with stage I–III CRC, high-dose metformin improved CRC-specific mortality (HR = 0.44, 95% CI = 0.20–0.95) [80]. In a meta-analysis, Meng et al. demonstrated that metformin improved OS rather than CRC-specific survival in patients who also had DM [81]. Yu et al. performed an umbrella review assessing the robustness and validity of studies investigating the potential anticancer effects of metformin [33]. CRC OS was strongly associated with metformin use. Because metformin only transiently causes cell cycle arrest by upregulating AMPK and promoting oxidative stress, biguanide should act synergistically with chemotherapy to induce cell death in CRC.

However, the evidence on whether metformin improves cancer prognosis is mixed (Table 4B). Singh et al. summarized the results of a prospective clinical trial from the North Central Cancer Treatment Group N0147 (Alliance), which investigated the effects of metformin on outcomes in patients with stage III CC receiving curative resection and adjuvant chemotherapy, but no significant effects were observed [11]. A 2019 sub-analysis of the TOSCA study, which comprised 3759 patients with high-risk stage II or III CC, indicated that metformin use in combination with fluoropyrimidine–oxaliplatin chemotherapy had no significant effects on rates of OS (HR = 1.51, 95% CI = 0.48–4.77) or relapse-free survival (HR = 1.56, 95% CI = 0.69–3.54) [7]. A nationwide registry-based study including 25,785 patients also reported no association between metformin use and CRC prognosis [82]. Large-scale trials

are necessary to establish definitive conclusions regarding whether metformin improves CRC prognosis.

Limitations

Because this article is a narrative review, we focused on analyzing various aspects of representative studies. Although several researchers have emphasized the significance of their results in their conclusions, the 95% CIs and significance levels (α) were inconsistent among the articles (or not included). Benjamin et al. [83] proposed changing the default *P*-value threshold for statistical significance from 0.05 to 0.005 because a large number of false positives was found among results with statistical significance with $P < 0.05$. The proposal did not address multiple-hypothesis testing, *P*-hacking, publication bias, or other biases. However, reducing the *P*-value threshold can provide solutions to these other problems. Therefore, we suggest cautiously interpreting the results from research included in this review that do not meet the $P < 0.005$ standard or include only a 95% confidence interval.

Conclusion

In this narrative review, we demonstrated that associations between DM, hyperglycemia, and CRC are manifold and heterogeneous and identified the critical linkages between DM and CRC. Further studies are warranted to elucidate the potential role of hyperglycemia on outcomes in patients with DM. The effect of metformin use on reducing adenoma formation and improving prognosis also requires more cumulative confirmatory evidence. With the rise in the global mortality rates of CRC and DM, cancer prevention strategies and public health intervention should be promoted, and a credible framework for the therapeutic agenda should be comprehensively implemented.

Ethics approval and consent to participate

As this study is a narrative review, ethics approval was not necessary after consulting the Institutional Review Board of Kaohsiung Medical University Hospital.

Consent for publication

As this study is a narrative review, consent for publication from patients was not applicable after consulting the Institutional Review Board of Kaohsiung Medical University Hospital.

Availability of data and material

The datasets supporting this manuscript are included within the article. All raw data can be acquired from the corresponding author.

Declaration of Competing Interest

The authors declare that they have no competing interests.

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Authors' contributions

Hsiu-Chung Cheng: Conceptualization, Resources, Data curation, Writing - Original Draft. **Tsung-Kun Chang:** Data curation, Resources, Writing - Original Draft. **Wei-Chih Su:** Formal analysis, investigation, Resources. **Hsiang-Lin Tsai:** Validation, Writing - Review & Editing. **Jaw-Yuan Wang:** Writing - Review & Editing, Visualization, Supervision, Project administration.

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