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Implications of Type II Diabetes Mellitus on Gastrointestinal Cancers

Diana H. Yu and M. Mazen Jamal
Section of Gastroenterology, Long Beach Veterans Affairs (VA) Healthcare System
Long Beach, California
Department of Medicine, University of California Irvine College of Medicine
Irvine, California
United States of America

1. Introduction

The rapid growth of the prevalence of Type II Diabetes Mellitus (DM) and its complications among adults has become a major public health problem that is approaching epidemic proportions worldwide. The world prevalence of diabetes among adults is estimated to be 285 million in 2010, and this number is projected to reach 439 million by 2030 (Shaw et al., 2010). While the pathogenesis of hyperglycemia in Type I DM is secondary to lack of insulin due to islet destruction, the hyperglycemia in Type II DM results from complex genetic interactions, the expression of which is modified by environmental factors such as increased age, reduced physical activity and obesity (Inzucchi & Sherwin, 2007). The over-production of insulin and the influence of hyperinsulinemia in enhancing free or bioavailable concentrations of insulin-like growth factor-1 (IGF-1) have been postulated to increase carcinogenesis through a tyrosine kinase growth factor cascade in enhancing tumor cell proliferation (Campbell et al., 2010; Giovannucci, 1995; McKeown-Eyssen, 1994; Moore, 1998).

Type II DM has been demonstrated by numerous epidemiologic studies to be associated with increased risk of many gastrointestinal cancers: esophageal adenocarcinoma, colorectal cancer, pancreatic cancer, biliary tract cancers (primary gallbladder carcinoma, extrahepatic/intrahepatic cholangiocarcinoma) and hepatocellular carcinoma. This review focuses on the expanding body of clinical evidence that supports the association between Type II DM and the increased risk of gastrointestinal cancers. Implications of Type II DM on each respective gastrointestinal cancer are divided into proposed etiology and pathophysiology, and review of epidemiologic studies to support the suggestion that Type II DM independently increase the risk of gastrointestinal cancers.

2. Implication of Type II DM on esophageal adenocarcinoma

2.1 Etiology and pathophysiology

One of the postulated mechanisms to explain the association between Type II DM and esophageal adenocarcinoma is that the metabolic changes associated with DM and

adiposity, such as hyperinsulinemia, establishes a hormonal environment which promotes the development of nascent tumors (Calle & Kaaks, 2004; Neale et al., 2009).

Insulin is the hormone integral to the 'metabolic hormonal hypothesis,' proposed by Calle and colleagues. Insulin activates the insulin receptor, and consequently the intracellular signaling cascades with mitogenic and anti-apoptotic effects. Insulin also promotes synthesis and activity of insulin-like growth factor-1 (IGF-1), a peptide hormone with similar structure of insulin, which regulates cellular proliferation in response to available energy and reserves (Calle & Kaaks, 2004). *In vitro* studies have clearly established that both insulin and IGF-1 act as growth factors that promote cell proliferation and inhibit apoptosis (Ish-Shalom et al., 1997; Khandwala, 2000; Lawlor & Alessi, 2001; Le Roith, 2000; Prisco et al., 1999).

As hyperinsulinemia is positively associated with the risk of esophageal adenocarcinoma, association with type II DM, "a proxy for pre-existing hyperinsulinemia," was observed independently of other obesity-related factors by Neale and colleagues (Neale et al., 2009).

2.2 Epidemiologic studies

In a large population-based case-control study in Australia, Neale and colleagues observed consistently higher risks of esophageal adenocarcinoma among those with diabetes within each category of Body Mass Index (Neale et al., 2009). People with diabetes who were also obese were at a 3.5 fold higher risk of esophageal adenocarcinoma than those with neither risk factor (Odds Ratio (OR) 3.55, 95% Confidence Interval (CI) 1.87-6.76). Esophageal adenocarcinoma risks were somewhat lower in those with either obesity or diabetes alone (Obesity: OR 2.67, 95% CI 1.8-3.96; Diabetes: OR 1.86, 95% CI 0.65-5.31).

Hemminki and colleagues also conducted a large population-based study of 125,126 in Sweden, which assessed cancer risks in patients who were hospitalized for Type II DM. For the entire follow-up period (All: 1 year or 5 years), the risk for esophageal cancer was significant in Type II diabetic patients. Standardized incidence ratio (SIR) for esophageal cancer was 2.19 (95% CI 1.83-2.59). The association between number of hospitalizations and esophageal cancer was also observed (Hemminki et al., 2010).

The case-control study by Neale and colleagues is consistent in demonstrating that Type II diabetic patients have about two-fold increased risk of esophageal adenocarcinoma. Hemminki et al. also supported the finding that Type II DM is associated with about two-fold increased risk of esophageal cancer overall; however, no distinction was made between adenocarcinoma and squamous cell carcinoma.

3. Implication of Type II DM on colorectal cancer

3.1 Etiology and pathophysiology

Obesity, reduced physical activity and abdominal distribution of adiposity, which are determinants of the metabolic syndrome, have been implicated in increased risk of colorectal cancer (Giovannucci, 2007; Glade, 1999). Hyperglycemia and hyperinsulinemia, which are the underlying metabolic defects of the metabolic syndrome and are especially pronounced during the early state of Type II DM, have been proposed as mediators for association between metabolic syndrome and colorectal cancer (Campbell et al., 2010; Giovannucci, 1995; McKeown-Eyssen, 1994).

Chronic hyperinsulinemia of Type II DM leads to insulin resistance as a metabolic adaptation to increased circulating levels of free fatty acids released from adipocytes. Increased free fatty acids leads to reduced capacity of livers, muscle and other tissues to absorb, store and metabolize glucose (Bergman & Ader, 2000). In addition to free fatty acids, adipocytes also release endocrine signaling factors, adiponectin and leptin, which play a role in regulation of insulin sensitivity in liver, muscle and other tissues (Havel, 2002). Furthermore, insulin positive feedback influences levels of leptin, a mitogenic adipocytokine, which has been demonstrated to be associated with cancers of the colon, breast and prostate (Stattin et al., 2003; Tessitore et al., 2000).

3.2 Epidemiologic studies

A 2005 meta-analysis of epidemiologic studies reported that DM was associated with a moderate increased risk of CRC overall, with almost identical associations when men and women were analyzed separately (Larsson et al., 2005). Analysis of 15 studies (six case-control and nine cohort studies), with 2,593,935 participants, showed that diabetes was associated with an increased risk of colorectal cancer when compared to non-diabetic controls (Pooled RR of colorectal cancer incidence = 1.3, 95% CI 1.20-1.40), without heterogeneity between studies. In a Singapore Chinese Health Study of diabetic cohort, with distinct body type and lifestyle profiles from those of Western population, Type II DM was also statistically significantly associated with colorectal cancer risk in both men (RR = 1.5, 95% CI = 1.2-2.1) and women (RR = 1.4, 95% CI = 1.0-1.9) (Seow et al., 2006) [Table 1].

More recent studies, however, consistently demonstrate stronger associations for men than for women (Inoue et al., 2006; Kuriki et al., 2007; Limburg et al., 2006; Seow et al, 2006;) [Table 1]. Many studies which examine the association between Type II DM and CRC published since the 2005 meta-analysis by Larsson, analyze statistics in men and women separately in the same study, which suggest that the association among women is not as significant relative to men.

A more recent large, prospective cohort-study by Campbell et al. demonstrated the association between Type II DM and CRC among men (RR 1.24, 95% CI 1.08-1.44), but not among women (RR 1.01, 95% CI 0.82-1.23) (Campbell et al., 2010). Limburg and colleagues have also supported a statistically significant relationship between Type II DM and CRC (especially proximal colon CRC vs. distal CRC) in men, but not statistically significant in women. Over 19,158 person-years of follow-up, 51 incident CRC cases were identified within the type 2 DM cohort of 1,975, while only 36.8 cases were expected based on data from the general population (Standardized Incidence Ratio (SIR) = 1.39, 95% CI 1.03-1.82). In men, Type II DM was associated with increased overall (SIR = 1.67, 95% CI 1.16-2.33) and proximal (SIR = 1.96, 95% CI 1.16-3.10) CRC risks, with statistically not significant increase in distal CRC risk. Conversely, in women, Type II DM was not a risk factor for overall, proximal or distal CRC (SIR = 1.03, 95% CI 0.60-1.66; SIR = 1.17, 95% CI 0.58-2.09; and SIR = 0.74, 95% CI 0.24-1.72, respectively) (Limburg et al., 2006) [Table 1].

Large population-based case-control studies conducted by Ren et al. in China, and by Kuriki et al. and Inoue et al. in Japan, established that association between Type II DM and CRC is statistically significant in both men and women; however, Type II DM women showed less pronounced risk for CRC compared to Type II men (Inoue et al., 2006; Kuriki et al., 2007: Ren et al., 2009). Kuriki and colleagues studied the associations between Type II DM and

multi-site cancer risks in a case-control study of 11,672 cancer cases (5341 men, 6331 women) and 47,768 cancer-free controls. Adjusted for confounding factors such as age, BMI, alcohol, smoking, physical exercise, bowel movement, family history of CRC, family history of DM, vegetable intake and dietary restriction, past/present history of diabetes was associated with increased CRC risk for both men and women (OR=1.3, 95% CI 1.0-1.65, OR=1.13, 95% CI 0.72-1.76, respectively) (Kuriki et al., 2007). A more significant association between Type II DM and CRC was observed by Ren and colleagues in their population-based case-control study conducted in China (SIR = 1.82, 95% CI 1.23-2.4 in Type II DM men, SIR = 1.36, 95% CI 0.85-1.88 in Type II DM women) (Ren et al., 2009). Inoue and colleagues have observed moderately increased risk of colon CA in diabetic men (HR 1.36, 95% CI 1.0-1.85) and rectal CA in diabetic women (HR 1.65, 95% CI 0.8-3.39), without statistically significant increase of colon CA in diabetic women and rectal CA in diabetic men.

Study	Control	Case	Adjusted Risk for Colorectal Cancer	Adjustment
Seow et al.	Non-Diabetic (Cases of CRC) 55,851 (546)	Diabetic (Cases of CRC) 5,469 (90)	RR = 1.5 (95% CI 1.2-1.8)	Age, Sex, Dialect group, Education, Body Mass Index, Smoking, Alcohol, Familial Hx of CRC, Physical activity
Inoue et al.	Non-Diabetic † (Cases of Colon CA) 43,451 (445)	Diabetic † (Cases of Colon CA) 3,097 (46)	HR = 1.36 (95% CI 1.0-1.85)	Age, Study area, Hx of cerebrovascular disease, Hx of ischemic heart disease, Smoking, Alcohol, Body Mass Index, Physical activity, Vegetable intake, Coffee intake
	Non-Diabetic ‡ (Cases of Colon CA) 49,652 (293)	Diabetic ‡ (Cases of Colon CA) 1,571 (10)	HR = 0.83 (95% CI 0.42-1.61)	
	Non-Diabetic † (Cases of Rectal CA) 43,451 (228)	Diabetic † (Cases of Rectal CA) 3,097 (15)	HR = 0.8 (95% CI 0.47-1.36)	
	Non-Diabetic ‡ (Cases of Rectal CA) 49,652 (145)	Diabetic ‡ (Cases of Rectal CA) 1,571 (8)	HR = 1.65 (95% CI 0.8-3.39)	
Limburg et al.	Non-Diabetic † (EI of CRC) Not Specified (20.4)*	Diabetic † (OI of CRC) 997 (34)	SIR = 1.67** (95% CI 1.16-2.33)	
	Non-Diabetic ‡ (EI of CRC) Not Specified (16.4)*	Diabetic ‡ (OI of CRC) 978 (17)	SIR = 1.03** (95% CI 0.6-1.66)	
Kuriki et al.	Without CRC† (Case of DM) 13,254 (945)	With CRC† (Case of DM) 686 (76)	OR = 1.3 (95% CI 1.0-1.68)	Age, Body Mass Index, Alcohol, Smoking, Physical exercise, Bowel movement, Family Hx of CRC, Family Hx of DM, Vegetable intake, Dietary restriction
	Without CRC‡ (Case of DM) 32,789 (780)	With CRC‡ (Case of DM) 527 (22)	OR = 1.13 (95% CI 0.72-1.76)	
Ren et al.	Non-Diabetic † (EI of CRC) Not Specified (20.3)*	Diabetic † (OI of CRC) 3,792 (37)	SIR = 1.82** (95% CI 1.23-2.4)	
	Non-Diabetic ‡ (EI of CRC) Not Specified (19.8)*	Diabetic ‡ (OI of CRC) 4146 (27)	SIR = 1.36** (95% CI 0.85-1.88)	

RR = Risk Ratio, HR = Hazard Ratio, SIR = Standardized Incidence Ratio, OR = Odds Ratio
DM = Diabetes Mellitus, CRC = Colorectal Cancer, Hx = History, EI = Expected Incidence, OI = Observed Incidence
† Men ‡ Women
* Number of EI calculated according to age & gender-specific incidence rate of general population
** Calculated as ratio of Observed Incidence cases to Expected Incidence cases

Table 1. Type II DM and Colorectal CA

These studies, taken as a whole, suggest Type II DM is associated with a moderately increased risk of CRC overall, with more recent studies consistently demonstrating stronger associations for men than for women.

4. Implication of Type II DM on pancreatic cancer

4.1 Etiology and pathophysiology

The precise etiology of pancreatic cancer remains unclear. Several environmental factors have been implicated, but evidence of a causative role exists only for tobacco use.

Many epidemiologic studies have reported a positive association between DM and pancreatic cancer risk, with concern that diabetes may be a consequence, rather than a cause (Noy & Bilezikian, 1994). However, other studies have demonstrated an association between elevated plasma glucose, insulin and C-peptide levels - characteristics of long-standing DM – with increased risk for pancreatic cancer (Batty et al., 2004; Gapstur et al., 2000; Jee, et al., 2005; Michaud, et al., 2007; Stattin, et al., 2007).

Some studies have demonstrated an increased incidence of pancreatic cancer among patients with chronic pancreatitis or history of DM (Batty et al., 2009; Genkinger et al., 2009; Hildalgo, 2010; Landi, 2009; Lowenfels & Maisonneuve, 2006). Though less conclusive, there is also evidence that chronic cirrhosis, high-cholesterol diet and previous cholecystectomy are associated with an increased incidence of pancreatic cancer (Batty et al., 2009; Genkinger et al., 2009; Hildalgo, 2010; Landi, 2009; Lowenfels & Maisonneuve, 2006).

Considerable number of recent epidemiologic studies suggests that DM may be a predisposing factor in pancreatic carcinogenesis (Gapstur et al., 2000).

4.2 Epidemiologic studies

A meta-analysis conducted by Everhart et al. has shown that a history of diabetes for greater than or equal to 5 years increases the incidence of pancreatic cancer by twofold (Everhart & Wright, 1995). Among 20 studies included in meta-analysis, 18 demonstrated a positive association between preexisting diabetes and the occurrence of pancreatic cancer. The pooled Relative Risk (RR) of 20 epidemiologic studies for those diabetes was diagnosed at least 1 year prior to either diagnosis of pancreatic cancer or mortality was 2.1 with 95% CI of 1.6-2.8. In an analysis requiring a 5-year duration of diabetes resulted in similar results, with RR of 2.0 (95% CI 1.2-3.2) in 11 epidemiologic studies [Table 2].

In a hospital based case-control study, Bonelli et al. have demonstrated that the risk of pancreatic cancer was increased by 6.2 fold in patients with diabetes, which necessitated insulin therapy for greater than 5 years (Bonelli et al., 2003). Jamal and colleagues further supported these findings with their large population-based case-control study of 1,172,496 patients, by demonstrating that occurrence of pancreatic cancer was increased by threefold in DM patients compared to controls (frequency of pancreatic cancer in DM subjects 0.9% compared to control subjects 0.3% with OR:3.22, 95% CI: 3.03-3.42) (Jamal et al., 2009) [Table 2].

A more recent three large case-control studies conducted by Li and colleagues have shown that diabetes is associated with 1.8 fold risk of pancreatic cancer (95% CI: 1.5-2.1), adjusted for age, sex, race, education, smoking, alcohol consumption and Body Mass Index (BMI). Risk estimates decreased with increasing years with diabetes. Among diabetics, risk was higher in insulin users vs. non-users (OR: 2.2, 95%CI 1.6-3.7). Insulin

use of >10 years was associated with reduced risk of pancreatic cancer (OR: 0.5 95% CI: 0.3-0.9). Lastly, Hispanic/Latino-American men and Asian-Americans had higher risks of diabetes-associated pancreatic cancer when compared to Caucasian-Americans and African-Americans, but the differences were not statistically significant (Li et al., 2011) [Table 2].

Study	Control	Case	Adjusted Risk for Pancreatic Cancer	Adjustment
Jamal et al.	Non-Diabetic (% with pancreatic CA) 836,283 (0.3)	Diabetic (% with pancreatic CA) 278,761 (0.9)	OR = 3.22 (95% CI 3.03-3.42)	Smoking, Obesity, Pancreatitis and other Pancreatic disorders
Li et al.†	Without Pancreatic CA (% with DM) 5113 (11)	With Pancreatic CA (% with DM) 2192 (20.4)	OR = 1.8 (95% CI 1.5-2.1)	Age, Sex, Race, Education, Smoking, Alcohol, Body Mass Index, Study site
Gapstur et al.‡	Non-Diabetic (No. of pancreatic CA mortality) 16,158 (30)	Diabetic (No. of pancreatic CA mortality) 2,578 (23)	RR = 2.15 (95% CI 1.22-3.8)	Age, Race, Categories of postload plasma glucose [ ], Smoking, Body Mass Index
Everhart et al.¶	NA	NA	DM (1yr)* RR= 2.1 (95% CI 1.6-2.8) DM (5yr)** RR= 2.0 (95% CI 1.2-3.2)	Age (Each epidemiologic study included in Meta-analysis with own variables)
Calle et al.	Non-Diabetic (No. of pancreatic CA mortality) 1,035,758 (2953)	Diabetic (No. of pancreatic CA Mortality) 53,828 (249)	RR = 1.48 (95% CI 1.3-1.68)	Age, Race, Smoking, Family Hx of pancreatic CA, Body Mass Index, Education

OR = Odds Ratio, RR = Risk Ratio, CI = Confidence Interval, CA = Cancer, NA = Non- applicable, Hx = History, DM = Diabetes Mellitus, [ ] = Concentration, No. = Number, yr = year

† Data pooled from 3 case-control studies (M.D. Anderson Cancer Center Study, University of California San Francisco Bay Area Study, National Cancer Institute Study)

‡ Non-diabetic designated to participants with postload plasma glucose [ ] ≤ 119mg/dL (6.6mmol/L). Diabetic designated to participants with postload plasma glucose [ ] ≥ 200mg/dL (11.1mmol/L)

Meta-analysis: Pooled RR of 20 epidemiologic studies* 11 epidemiologic studies **

Table 2. Type II DM and Pancreatic CA

Gapstur and colleagues have also demonstrated a positive association between post-load plasma glucose level and risk of pancreatic cancer mortality. Risk was 2.2 fold higher (RR

2.15 CI 1.22-3.8, p 0.01) for participants whose post load plasma glucose level was at least 200mg/dL at baseline compared to those with less or equal to 119mg/dL, adjusted for age, race, cigarette smoking status and BMI. This association was independent of other known and suspected pancreatic cancer risk factors such as age, race, cigaretts smoking and BMI (Gapstur et al., 2000) [Table 2].

Lastly, Calle et al. have also concluded from their study, after 12 years of follow-up in 1,089,586 men and women, that a history of self-reported diabetes was associated with increased pancreatic cancer mortality RR = 1.48 (95% CI 1.3-1.68) [Table 2]. This association was similar in men RR = 1.49 (95% CI 1.25-1.77) and women RR = 1.51 (95% CI 1.24-1.85). (Calle et al., 1998) [Table 2].

These studies, taken as a whole, suggest Type II DM is independently associated with about two-fold increased risk in pancreatic cancer. This finding is consistent throughout all studies which adjusted for tobacco use, which remains to be the only environmental factor that plays a causative role in the risk of pancreatic cancer.

5. Implication of Type II DM on biliary tract cancer (primary carcinoma of gallbladder and extrahepatic/intrahepatic cholangiocarcinoma)

5.1 Etiology and pathophysiology

Type II DM is associated with insulin resistance, compensatory hyperinsulinemia and up-regulated level of insulin-like growth factors (IGFs). Cai and colleagues have recently demonstrated that IGFs may stimulate cholangiocyte growth through cellular proliferation and inhibition of apoptosis (Cai et al., 2008). Furthermore, the integral role IGFs may play in the carcinogenesis of cholangiocytes is supported by *in vitro* and *in vivo* studies (Alvaro et al., 2006).

The etiology of primary gall bladder carcinoma is not well understood. However, several factors have been postulated to place patients at a greater risk. These risk factors include gallstone disease, obesity, female sex, tobacco use and an anomalous pancreaticobiliary ductal union (Jones, 1990; Strom et al., 1995). Some international population-based studies have also shown that diabetes is independently associated with a higher risk of gallstones, which is one of the major risk factors for primary carcinoma of the gallbladder (Festi et al., 2008; Shebl et al., 2010).

In a recent study by Biddinger and colleagues, the mechanistic link between the well-documented association between gallstones and the metabolic syndrome has been proposed (Biddinger et al., 2008). Their study using the LIRKO mouse model (mice with isolated hepatic insulin resistance created by liver-specific disruption of the insulin receptor), showed that hepatic insulin resistance leads to increased biliary cholesterol secretion and cholesterol gallstone formation, both of which are features of the human metabolic syndrome (Attili et al., 1997; Bennion & Grundy, 1975; Shaffer & Small, 1977). These effects are due to disinhibition of the forkhead transcrtiption factor (FoxO1), which drives the expression of the biliary cholesterol transporters (Abcg5 and Abcg8), in addition to the enzymes of gluconeogenesis (Biddinger et al., 2008).

5.2 Epidemiologic studies

In a large population-based case-control study conducted among 1,172,496 American Veterans, Jamal and colleagues have found that Type II DM was associated with an increased

risk of gallbladder cancer. The risk of gallbladder (OR 2.2, 95%CI 1.56-3) cancer was increased by two-fold in diabetic patients when compared to controls (Jamal et al., 2009) [Table 3]. A case-control study using a large United Kingdom primary care database, Grainge et al. also demonstrated that the relative risk of gallbladder cancer in diabetic patients compared to non-diabetic controls was 1.43 (95% CI: 0.81-2.52) (Grainge et al., 2009) [Table 3].

A similar analysis was performed by investigators, Shebl and colleagues in a population-based case-control study of 627 biliary tract cancers, 1037 biliary tract stones, and 959 controls in Shanghai, China. Independent of BMI, diabetes was associated with significantly increased risks of gallbladder cancer and biliary stones, OR 2.6 (95% CI 1.5-4.7) and 2.0 (95% CI 1.2-3.3), respectively. Furthermore, about 60% of the effect of diabetes on biliary tract cancer was mediated in part by gallstones and 17% by high-density lipoprotein (HDL). However, no significant association was found with extrahepatic biliary cancer and cancer of Ampulla of Vater. (Shebl et al., 2010) [Table 3].

Study	Control	Case	Adjusted OR for Biliary Tract Cancer	Adjustment
Jamal et al.†‡	Non-Diabetic (% with Gallbladder CA) 836,283 (0)	Diabetic (% with Gallbladder CA) 278,761 (0.03)	OR = 2.2 (95% CI 1.56-3.0)	Gallstone disease, Smoking, Obesity
	Non-Diabetic (% with Extrahepatic Biliary CA) 836,283 (0.02)	Diabetic (% with Extrahepatic Biliary CA) 278,761 (0.1)	OR = 2.1 (95% CI 1.61-2.53)	
Grainge et al.†‡	Without Gallbladder CA (% DM) 5760 (5.9)	With Gallbladder CA (% DM) 5760 (8.7)	OR = 1.43 (95% CI 0.81-2.52)	Sex, Age
	Without Cholangiocarcinoma (% DM) 5760 (5.9)	With Cholangiocarcinoma (% DM) 372 (9.4)	OR = 1.48 (95% CI 1.0-2.17)	
Shebl et al.†	Without Gallbladder CA (% DM) 902 (7.54)	With Gallbladder CA (% DM) 367 (13.9)	OR = 2.63 (95% CI 1.47-4.68)	Age, Sex, Education, Diabetes duration, Body Mass Index, Waist-to-hip ratio, Aspirin use
Welzel et al.‡	Without ECC (% DM) 102,782 (22.1)	With ECC (% DM) 549 (30.1)	OR = 1.5 (95% CI 1.3-1.8)	Age, Sex, Race, Geographic location
	Without ICC (% DM) 102,782 (22.1)	With ICC (% DM) 535 (33.1)	OR = 1.8 (95% CI 1.5-2.1)	
Tao et al.‡	Without ECC (% DM) 380 (9.5)	With ECC (% DM) 129 (18.6)	OR = 3.2 (95% CI 1.7-5.9)	Age, Sex, DM, Cholelithiasis, Hx of Cholecystectomy
	Without ICC (% DM) 380 (9.5)	With ICC (% DM) 6.1 (4.9)	NA	

OR = Odds Ratio, CI = Confidence Interval, CA = Cancer, NA = Non-applicable
Hx = History, DM = Diabetes Mellitus, ECC = Extrahepatic Cholangiocarcinoma
ICC = Intrahepatic Cholangiocarcinoma
† Gallbladder CA
‡ Extrahepatic and/or Intrahepatic Cholangiocarcinoma

Table 3. Type II DM and Biliary Tract CA

However, several other studies have shown that there is significant association between Type II DM and bile duct cancers. Jamal et al. in the same large population-based case-control study, described above, showed that extrahepatic biliary cancer was increased by two-fold in diabetic patients (OR 2.1, 95% 1.61-2.53) (Jamal et al., 2009). Grainge and colleagues, in their large UK study, described above, also support the finding of increased risk of cholangiocarcinoma in diabetic patients compared to non-diabetic controls (RR = 1.48, 95% CI: 1.0-2.17) (Grainge et al., 2009) [Table 3].

Welzel et al. further demonstrated that Type II DM was significantly more common among both Extrahepatic Cholangiocarcinoma (ECC) and Intrahepatic Cholangiocarcinoma (ICC). The study examined the prevalence of following risk factors for both ECC and ICC in patients age 65 years and older with diagnosis of ECC or ICC using the SEER (Surveillance, Epidemiology, and End Results) database in the United States: Biliary cirrhosis, cholelithiasis, choledocholithiasis, cholecystitis, cholecystectomy, alcoholic liver disease, liver cirrhosis, Type II DM, thyrotoxicosis and chronic pancreatitis. Prevalence of Type II DM was significantly higher in patients with ECC compared to those without ECC (OR = 1.5, 95% CI 1.3-1.8). Similar result was found in patients with ICC compared to those without ICC (OR = 1.8, 95% CI 1.5-2.1) [Table 3].

A similar study was conducted by investigators in China by Tao and colleagues, who also supported Welzel's findings that Type II DM had a positive association with ECC (OR = 3.2, 95% CI 1.7-5.9), adjusted for age, gender, history of cholelithiasis and cholecystectomy. However, in this Chinese population-based study, an inverse association between Type II DM and ICC were reported (increased DM cases among patients with ICC than those without ICC) (Tao et al., 2009) [Table 3].

6. Implication of Type II DM on hepatocellular carcinoma

6.1 Etiology and pathophysiology

The main etiology of hepatocellular carcinoma (HCC) is chronic infection with hepatitis B and hepatitis C viruses. However, there are other important factors that contribute to the international burden of HCC. Among these are obesity, diabetes, non-alcoholic steatohepatitis (NASH) and dietary exposures (Blonski et al, 2010). Diabetes is a part of the metabolic syndrome that is characterized by insulin resistance and is thought to predispose to nonalcoholic fatty liver disease (NAFLD), including its more severe form, nonalcoholic steatohepatitis (NASH) (El-Serag, et al., 2006). Diabetes has also been identified as an independent factor for disease progression and for more advanced liver disease in patients with NAFLD.

HCC as a complication of diabetes-associated NASH has been described (Di Bisceglie et al., 1998; El-Serag et al., 2001) and diabetes has been found to be prevalent in patients with HCC and cryptogenic cirrhosis (Marchesini et al., 1999; Matteoni et al., 1999). However, the pathophysiology underlying the increased risk of chronic nonalcoholic liver disease and HCC with diabetes is uncertain. Proposed pathyphysiology involves increased insulin resistance in NAFLD patients compared with control subjects (Marchesini et al., 1999). Insulin resistance facilitates peripheral lipolysis, decreases mitochondrial beta-oxidation of fatty acids and increases accumulation of free fatty acids in the liver, which can lead to NAFLD (Chitturi & Farrell, 2001; Pessayre et al., 2001). Recent studies have shown that

HCC can result as a consequence of DM-related NASH (Cotrim et al., 2000; Shimada et al., 2002; Zen et al., 2001).

6.2 Epidemiologic studies

In a large retrospective cohort study of veteran patient populations (DM cohort: 173,643. Control: 650,620), El-Serag and colleagues have shown that the incidence of chronic nonalcoholic fatty liver disease (NAFLD) was significantly higher among patients with diabetes compared to control patients (Incidence rate: 18.13 vs. 9.55 per 10,000 person-years, respectively). Corresponding results were obtained for higher rates of HCC among diabetic patients compared to non-diabetic patients (incidence rate: 2.39 vs. 0.87 per 10,000 person-years, respectively), supporting previously published studies with positive association between Type II DM and HCC (El-Serag et al., 2004).

Furthermore, in a recent systematic review of 13 case-control studies, 11 supported an association between diabetes and the development of HCC. Among the 13 case-control studies, subjects with diabetes were found to have a two-fold increase in the risk of HCC. This association was also appreciated amongst 12 cohort studies evaluated (El-Serag et al., 2006).

7. Conclusion

Type II Diabetes Mellitus and its complications is a growing public health problem worldwide. Increased morbidity and mortality associated with various gastrointestinal cancers as one of the complications of Type II DM holds strong public health and clinical relevance. There is a growing body of evidence suggesting that Type II DM and its metabolic defects (hyperinsulinemia and hyperglycemia) are associated with increased risk of various gastrointestinal cancers. Although further studies are required to definitively validate this association, the current understanding between Type II DM and gastrointestinal cancers warrants attention for its potential implications in the clinical practice of diabetic management and novel targeted cancer therapy.

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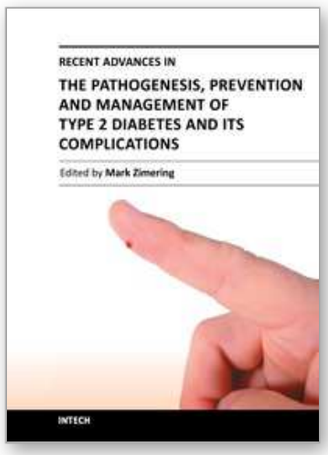

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Type 2 diabetes â€œmellitusâ€ affects nearly 120 million persons worldwide- and according to the World Health Organization this number is expected to double by the year 2030. Owing to a rapidly increasing disease prevalence, the medical, social and economic burdens associated with the microvascular and macrovascular complications of type 2 diabetes are likely to increase dramatically in the coming decades. In this volume, leading contributors to the field review the pathogenesis, treatment and management of type 2 diabetes and its complications. They provide invaluable insight and share their discoveries about potentially important new techniques for the diagnosis, treatment and prevention of diabetic complications.

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