Effect of insulin therapy and obesity on colon adenoma and advanced adenoma among type II diabetes mellitus population

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Abstract

Insulin is a debatable risk factor for colon adenoma (Ad) among type II diabetes mellitus (DM II) patients. Obesity is an important confounding variable. The study involved chart review of DM II patients undergoing screening colonoscopy. Study population was divided into obese [body mass index (BMI)≥30] and non-obese (BMI<30) groups which were further divided into insulin and non-insulin subgroup. Colonoscopy and pathology reports were used to calculate Ad detection rate (ADR) and AAd detection rate (AADR). A total of 538 subjects satisfied the inclusion and exclusion criteria. The study population composed of 52.8% obese and 47.2% non-obese subjects. Obese group had 28.9% insulin and 71.1% non-insulin subjects. Non-obese group composed of 29.9% insulin and 70.1% non-insulin subjects. ADR for non-obese insulin and non-insulin subgroup was 31.6% and 37.1% respectively. AADR for non-obese insulin and non-insulin subgroup was 13.2% and 11.2% respectively. ADR for obese insulin and non-insulin subgroup was 41.5% and 34.2% respectively. AADR for obese insulin and non-insulin subgroup was 15.9% and 16.3% respectively. Insulin exposure lacked statistically significant association with ADR or AADR among obese and non-obese DM II subjects.

Introduction

Colorectal cancer (CRC) is a result of malignant growth of epithelial cells of colon or rectum. Over 95% of CRC are believed to arise in benign adenomatous polyps that grow very slowly over many years.[1] Disrupting the classic adenoma-carcinoma sequence by polypectomy is the basis for offering screening colonoscopy to reduce the incidence of CRC.

There are multiple known risk factors for adenomatous colon polyps. Some of the risk factors like age (>50 years in general and >45 years for African Americans), race (African American), gender (male), dietary habits (red meat), lifestyle (sedentary/smoking/alcohol), past medical history of polyps/CRC/inflammatory bowel disease (IBD), syndromes like familial adenomatous polyposis (FAP)/hereditary non-polyposis colorectal cancer (HNPCC) and family history of CRC have been proven to increase the risk of adenoma (Ad) and CRC and therefore are taken into account before planning CRC screening strategy for patients.[2,3] Other factors like, obesity, diabetes mellitus (DM), insulin exposure have been debated over last few years and the evidence is not strong enough to have an impact on the current CRC screening and surveillance guidelines.[2,3]

The type II DM (DM II) population has been shown to have a higher incidence of colon Ad and advanced adenoma (AAd) related to endogenous hyperinsulinemia and high levels of insulin growth factor-1 (IGF-1).[4-7] Few studies have shown positive correlation between exogenous insulin exposure and colon Ad among the DM II population.[8] But none of these studies took obesity into consideration which we think is an important confounding variable in the interpretation of above study results.

The prevalence of overweight [body mass index (BMI) between 25 and 30 kg/m^2] and obesity (BMI of 30 kg/m^2 or higher) is on rise worldwide.[9] Consequently, DM II prevalence is expected to raise.[9] There is 30-70% increased risk of colon cancer in men who are obese, whereas the association is less consistent in women.[10] Similar trends exist for colorectal Ad, although the risk appears lower.[10] There is evidence to suggest obesity as an independent risk factor for colon Ad, AAd and CRC.[11,12]

Materials and Methods

The objective of the study was to determine the effect of exogenous insulin exposure on colon Ad and AAd among DM II subjects after controlling for the effect of obesity.

The study had retrospective design and was conducted at an urban teaching hospital. The study was approved by the Institutional Review Board.

The inclusion criteria were: patients who underwent outpatient screening colonoscopy over a time span of 18 months.

Screening Colonoscopy was defined as: i) patient 45 years of age or older; ii) absence of any gastrointestinal sign, or symptom(s); iii) absence of any personal history of colon cancer or polyps. The exclusion criteria were: i) family history (FH) of CRC; ii) past medical history (PMH) of CRC/FAP/HNPCC/IBD/colectomy; iii) incomplete colonoscopy (lack of cecum intubation); iv) poor quality of bowel preparation.

Study method

This was a retrospective study and no intervention or deviation from standard practice protocols for patients were done for the study purposes. It involved chart review of patients, who had undergone outpatient colonoscopy at our center over a time span of 18 months. A list of eligible patients with their names and medical record numbers was obtained from the medical records department. A study identifier was then given to each subject. The master list of eligible patients was deleted after data was collected and checked.

Each subject's electronic medical record was reviewed to extract relevant data (age, gender, race, weight, height, DM II, Insulin use, PMH of CRC/FAP/HNPCC/IBD or FH of CRC). Weight and height of the individual subjects was used to calculate respective BMI. Colonoscopy reports of each subject were reviewed to collect data related to bowel preparation, indication for colonoscopy, cecum intubation, number and size of polyps. Inclusion and exclusion criteria were then applied to the initial population. Study population was divided into Obese

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(BMI≥30) and non-obese (BMI<30) groups. Insulin exposure was defined as any DM II patient on insulin therapy irrespective of its dose, duration or use of other anti-diabetic medications. Medication list for each subject was reviewed to divide obese and non-obese groups into insulin and non-insulin subgroups. Pathology reports were reviewed to confirm the histology of resected polyps. AAd was defined as adenomatous polyp with size ≥1 cm, villous/dysplastic character on histology, or presence of 3 or more adenomatous polyps on colonoscopy. Ad detection rate (ADR): percentage of patients who have one or more adenomatous polyps detected during colonoscopy; and AAd detection rate (AADR): percentage of patients who have one or more advanced adenomatous polyps detected during colonoscopy) was then calculated for each category.

Statistical analysis

Microsoft Office for MAC (version 2011) was used to analyze data. Chi-square (for Race and Gender) and Mann-whitney U test (for Age and BMI) was were used to compare baseline population characteristics across insulin and non-insulin subgroups of obese and non-obese category. ADR and AADR for subgroups were compared using Chi-square tests. P value of less than 0.05 was used to determine statistical significance.

Results

A total of 538 subjects, with a mean age of 60.2 years and male to female ratio of 1:1.4 satisfied the inclusion criteria. The study population composed of 284 (52.8%) obese and 254 (47.2%) non-obese subjects. ADR for obese and non-obese group was 36.3% and 35.4% respectively. AADR for obese and non-obese group was 16.2 and 11.8% respectively. Obese group had 82 (28.9%) insulin and 202 (71.1%) non-insulin subjects. Non-obese group composed of 76 (29.9%) insulin and 178 (70.1%) non-insulin subjects. Baseline population characteristics for insulin and non-insulin subgroups of non-obese and obese groups have been summarized in Table 1 and 2 respectively. ADR for non-obese insulin and non-insulin subgroup was 31.6 and 37.1% respectively (P=0.40) (Table 3 and Figure 1). AADR for non-obese insulin and non-insulin subgroup was 13.2 and 11.2% respectively (P=0.66) (Table 3 and Figure 1). ADR for obese insulin and non-insulin subgroup was 41.5 and 34.2% respectively (P=0.24) (Table 4 and Figure 2). AADR for obese insulin and non-insulin subgroup was 15.9 and 16.3% respectively (P=0.92) (Table 4 and Figure 2).

Table 1. Baseline population characteristics for insulin and non-insulin subgroup of non-obese type II diabetes mellitus group [non-obese (BMI<30 Kg/m^2) (N=254)].

Population characteristics	Insulin subgroup (N=76)	Non-insulin subgroup (N=178)	P value
Gender, n (%)			0.065
Male	42 (55.3)	76 (42.3)	
Female	34 (44.7)	102 (57.3)	
Age in years; average (range)	61.2 (49-79)	61.7 (49-83)	0.254
BMI Kg/m^2; average (range)	25.8 (18.3-29.9)	26.0 (12.7-29.9)	0.490
Race, n (%)			0.040
Asian/Indian/Pacific Islander	5 (6.6)	35 (19.7)	
African American	53 (69.7)	119 (66.9)	
Hispanic	9 (11.8)	15 (8.4)	
White	8 (10.5)	8 (4.5)	
Others/Unknown	1 (1.4)	1 (0.5)	

Table 2. Baseline population characteristics for insulin and non-insulin subgroup of obese type II diabetes mellitus group [obese (BMI≥30 Kg/m^2) (N=284)].

Population characteristics	Insulin subgroup (N=82)	Non-insulin subgroup (N=202)	P value
Gender, n (%)			0.006
Male	40 (48.8)	64 (31.7)	
Female	42 (51.2)	138 (68.3)	
Age in years; average (range)	58.7 (44-80)	59.1 (45-84)	0.446
BMI Kg/m^2; average (range)	36.6 (30.1-50.5)	36.3 (30.1-65.7)	0.896
Race, n (%)			0.218
Asian/Indian/Pacific Islander	0 (0.0)	7 (3.5)	
African American	63 (76.8)	151 (74.8)	
Hispanic	8 (9.8)	23 (11.4)	
White	7 (8.5)	18 (8.9)	
Others/Unknown	4 (4.9)	3 (1.4)	

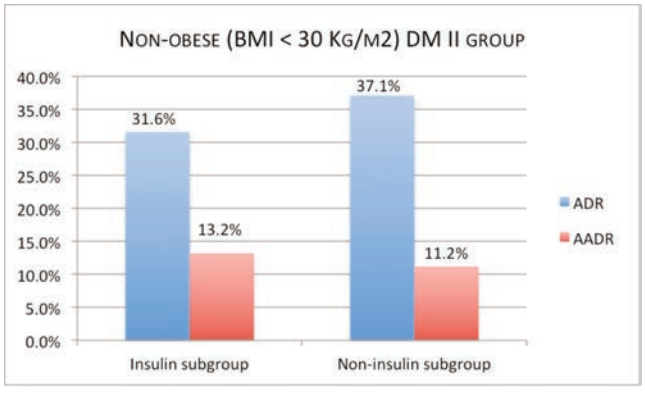

Figure 1. Adenoma detection rate and advanced adenoma detection rate for insulin and non-insulin subgroup of non-obese type II diabetes mellitus group.

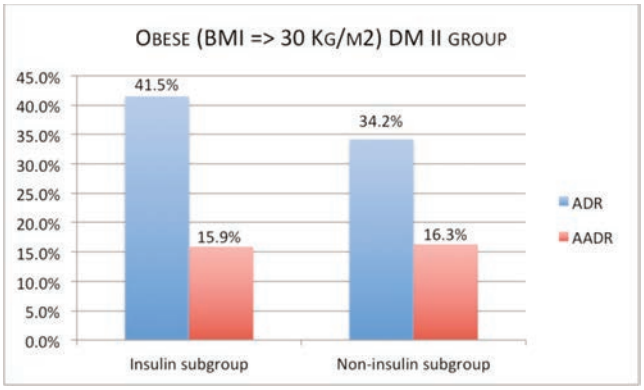

Figure 2. Adenoma detection rate and advanced adenoma detection rate for insulin and non-insulin subgroup of obese type II diabetes mellitus group.

Discussion and Conclusions

Many observational studies have shown positive association between DM II and CRC.[13] This association has been attributed to underlying hyperinsulinemia.[14,15] In early stages of DM II, endogenous hyperinsulinemia is seen in response to peripheral insulin resistance.[14] Insulin raises serum IGF-1 level, which is a regulator of growth and is known to play an important role in carcinogenesis through regulating cell proliferation and apoptosis.[16] Conditions with high circulating levels of IGF-1, such as acromegaly, have been associated with an increased risk of CRC.[17] The association between IGF-1 and adenomatous polyps is well supported.[18-21]

With growing evidence for reduction in micro-vascular complications with earlier introduction of insulin therapy,[22,23] there is a rapid increase in proportion of diabetics on insulin. Among patients with DM II, exogenous insulin therapy augments the endogenous insulin production, as shown by 24-hour plasma insulin levels.[24] Chung and colleagues reported a 3-fold increase in colorectal Ad risk in patients with at least one year of insulin therapy in a Korean-based population.[25] Schoen and colleagues, reported that the association between insulin and IGF-1 levels and colorectal Ad is more pronounced among AAd compared.[21] Furthermore, subjects with high fasting blood sugar and fasting insulin levels have been reported to have higher odds for colorectal adenoma.[26,27]

In last 20 years, the obesity prevalence has risen dramatically in the United States and other developed countries.[28,29] Abdominal obesity has been linked to insulin resistance and hyperinsulinemia, and consequently to the development of DM II.[30,31] BMI, a measure of overall obesity, is associated with increased risk of colon cancer in men, but has a weak or no association among women.[30] To our knowledge, there are no studies that have illustrated the association of exogenous insulin therapy among DM II with colon Ad and AAd after controlling for the confounding effect of obesity.

In our study, to elicit the independent association between exogenous insulin and colon Ad and AAd, we divided our population into non-obese (BMI<30 Kg/m^2) and obese (BMI≥30 Kg/m^2) group. Among non-obese group, the AADR was minimally higher for insulin subgroup (13.2%) than the non-insulin subgroup (11.2%). In contrast, the ADR was lower for the insulin subgroup (31.6%) than the non-insulin subgroup (37.1%). Regardless, both of them lacked statistical significance (P>0.05). Among obese group, the AADR for insulin subgroup (16.3%) was comparable to that of non-insulin subgroup (15.9%). In contrast the ADR was higher for insulin subgroup (41.5%) than the non-insulin subgroup (34.2%). Both of these trends also lacked any statistical significance (P>0.05).

Among non-obese group, there was statistical significant difference for the ethnic distribution of population across the two subgroups. Both groups were predominantly composed of African Americans (>65%) but non-insulin group had a bigger proportion of Asian/Indian/Pacific Islander population (19.7%). For the obese group, there was statistically significant difference for gender distribution across the two subgroups. Non-insulin subgroup was predominantly composed of women (68.3%) as compared to near equal distribution of gender in insulin subgroup. Rest of the parameters had comparable distribution across the insulin and non-insulin subgroups of both obese and non-obese groups (Table 1, 2).A few potential limitations need to be considered. Our study being retrospective in nature comes in with its possible selection and information bias. Lack of data on the dose and duration of insulin exposure among the study population limited our ability to confirm the underlying reason for lack of association between exogenous insulin exposure and colon Ad and AAd. Although, our study results cannot be generalized but in our population (predominantly African Americans), it failed to show any statistically significant association between exogenous insulin therapy and colon Ad and AAd among both obese and non-obese DM II. This observed trend is consistent with the current guidelines to consider DM II subjects as average risk population for CRC screening irrespective of their exogenous insulin exposure. Larger, prospective well-designed studies are required in future to confirm our findings.

Table 3. Adenoma detection rate and advanced adenoma detection rate for insulin and non-insulin subgroup of non-obese type II diabetes mellitus group [non-obese (BMI<30 Kg/m^2) (N=254)].

Dependent variable	Insulin subgroup (N=76)	Non-insulin subgroup (N=178)	P value
Adenoma, N (%)	24 (31.6)	66 (37.1)	0.400
Advanced adenoma, N (%)	10 (13.2)	20 (11.2)	0.667

Table 4. Adenoma detection rate and advanced adenoma detection rate for insulin and non-insulin subgroup of obese type II diabetes mellitus group [obese (BMI≥30 Kg/m^2) (N=284)].

Dependent variable	Insulin subgroup (N=82)	Non-insulin subgroup (N=202)	P value
Adenoma, n (%)	34 (41.5)	69 (34.2)	0.246
Advanced adenoma, n (%)	13 (15.9)	33 (16.3)	0.920

References

1. Bond JH. Clinical evidence for the adenoma-carcinoma sequence, and the management of patients with colorectal adenomas. Semin Gastrointest Dis 2000;11:176-84.
2. Ries LAG, Eisner MP, Kosary CL, et al. SEER cancer statistics review, 1975-2002. National Cancer Institute. Available from: http://seer.cancer.gov/csr/1975_2002/
3. Rex DK, Johnson DA, Anderson JC, et al. American College of Gastroenterology guidelines for colorectal cancer screening 2009 [corrected]. Am J Gastroenterol 2009;104:739-50.
4. Eddi R, Karki A, Shah A, et al. Association of type 2 diabetes and colon adenomas. J Gastrointest Cancer 2012;43:87-92.
5. Giovannucci E. Metabolic syndrome, hyperinsulinemia, and colon cancer: a review. Am J Clin Nutr 2007;86:s836-42.
6. Kim BC, Shin A, Hong CW, et al. Association of colorectal adenoma with components of metabolic syndrome. Cancer Causes Control 2012;23:727-35.
7. Elwing JE, Gao F, Davidson NO, et al. Type 2 diabetes mellitus: the impact on colorectal adenoma risk in women. Am J Gastroenterol 2006;101:1866-71.
8. Wong P, Weiner MG, Hwang WT, et al. Insulin therapy and colorectal adenomas in patients with diabetes mellitus. Cancer Epidemiol Biomarkers Prev 2012;21:1833-40.
9. Hjartåker A, Langseth H, Weiderpass E. Obesity and diabetes epidemics: cancer repercussions. Adv Exp Med Biol 2008;630:72-93.
10. Bardou M, Barkun AN, Martel M. Obesity and colorectal cancer. Gut 2013;62:933-47.
11. Okabayashi K, Ashrafian H, Hasegawa H, et al. Body mass index category as a risk

factor for colorectal adenomas: a systematic review and meta-analysis. Am J Gastroenterol 2012;107:1175-85
12. Yun KE, Chang Y, Jung HS, et al. Impact of body mass index on the risk of colorectal adenoma in a metabolically healthy population. Cancer Res 2013;73:4020-7.
13. Larsson SC, Orsini N, Wolk A. Diabetes mellitus and risk of colorectal cancer: a meta-analysis. J Nat Cancer Inst 2005;97: 1679-87.
14. Sandhu MS, Dunger DB, Giovannucci EL. Insulin, insulin-like growth factor-I (IGF-I), IGF binding proteins, their biologic interactions, and colorectal cancer. J Nat Cancer Inst 2002;94:972-80.
15. Giovannucci E. Insulin, insulin-like growth factors and colon cancer: a review of the evidence. J Nutr 2001;131:S3109-20.
16. LeRoith D, Baserga R, Helman L, et al. Insulin-like growth factors and cancer. Ann Int Med 1995;122:54-9.
17. Ritter MM, Richter WO, Schwandt P. Acromegaly and colon cancer. Ann Int Med 1987;106:636-7.
18. Renehan AG, Painter JE, Atkin WS, et al. High-risk colorectal adenomas and serum insulin-like growth factors. Br J Surg 2001;88:107-13.
19. Teramukai S, Rohan T, Lee K-Y, et al. Insulin-like growth factor (IGF)-I, IGF-binding protein-3 and colorectal adenomas in Japanese men. Jpn J Cancer Res 2002; 93:1187-94.
20. Renehan AG, Painter JE, O'Halloran D, et al. Circulating insulin-like growth factor II and colorectal adenomas. J Clin Endocrinol Metab 2000;85:3402-8.
21. Schoen RE, Weissfeld JL, Kuller LH, et al. Insulin-like growth factor-I and insulin are associated with the presence and advancement of adenomatous polyps. Gastroenterology 2005;129:464-75.
22. Ohkubo Y, Kishikawa H, Araki E, et al. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. Diabetes Res Clin Pract 1995;28:103-17.
23. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998;352: 837-53.
24. Garvey WT, Olefsky JM, Griffin J, et al. The effect of insulin treatment on insulin secretion and insulin action in type II diabetes mellitus. Diabetes 1985;34:222-34.
25. Chung YW, Han DS, Park KH, et al. Insulin therapy and colorectal adenoma risk among patients with Type 2 diabetes mellitus: a case-control study in Korea. Dis Colon Rectum 2008;51:593-7.
26. Pyo JH, Kim ES, Chun HJ, et al. Fasting blood sugar and serum triglyceride as the risk factors of colorectal adenoma in korean population receiving screening colonoscopy. Clin Nutr Res 2013;2:34-41.
27. Kim EH, Kim HK, Bae SJ, et al. Fasting serum insulin levels and insulin resistance are associated with colorectal adenoma in Koreans. J Diabetes Investig 2014; 5:297-304.
28. Hedley AA, Ogden CL, Johnson CL, et al. Prevalence of overweight and obesity among US children, adolescents, and adults, 1999-2002. JAMA 2004;291:2847-50.
29. Flegal KM, Carroll MD, Kit BK, et al. Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999-2010. JAMA 2012;307:491-7.
30. Vainio H, Kaaks R, Bianchini F. Weight control and physical activity in cancer prevention: international evaluation of the evidence. Eur J Cancer Prev 2002;11:S94-100.
31. Kahn BB, Flier JS. Obesity and insulin resistance. J Clin Invest 2000;106:473-81.