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# Association of Type 2 Diabetes with Colectomy; True or False?

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**ABSTRACT**

Colectomy is an invasive procedure indicated for various colon diseases. Surgical resection of the colon potentially affects glucose metabolism. The intestine secrets different hormones during digestion and controls absorption and metabolism of nutrients. There are gut-associated factors involved in glucose homeostasis. These include incretins, cholecystokinin, short-chain fatty acids, and non-esterified fatty acids. Type 2 diabetes mellitus (T2DM) is a major health problem with a constantly and dramatically increasing incidence and prevalence. In this review, the role of colon secretions and their cross-talk with gut microbiota in glucose metabolism and the pathophysiological aspects of alterations in bacterial endotoxin level, bile acid metabolism, and gut hormone secretion were highlighted. We have also noted the potential complications of colectomy in terms of glucose metabolism and homeostasis. All the clinical findings in previous studies documenting the association between T2DM post-colectomy were included as well.

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## Abbreviations

T2DM, Type 2 diabetes mellitus; IR, Insulin resistance; LPS, Lipopolysaccharide; GM, Gut microbiota; SCFA, Short-chain fatty acids; GLP-1, glucagon-like peptide-1; CCK, Cholecystokinin; CCKAR, Cholecystokinin A receptor; CCKBR, Cholecystokinin B receptor; GI, Gastrointestinal; TLR-4, Toll-like receptor 4; BA, Bile acid; TGR-5, Takeda G protein-coupled receptor 5; DF, Dietary fibers; GPR-43, G-protein coupled cell receptor 43; GPR-41, G-protein coupled cell receptor 41; FFAR-2, Free fatty acid receptor 2; FFAR-3, Free fatty acid receptor 3; PYY, Peptide tyrosine; Treg, Regulatory T cells; FMT, Fecal microbiota transplant; INF, Intestinal normal flora; SSI, Surgical site infections

## Introduction

Studies have shown a significant increase in type 2 diabetes mellitus (T2DM) among adults and adolescents (1). In 2013, approximately 382 million diabetic patients were diagnosed worldwide. This population is estimated to be more than 590 million by 2035 (2).

Due to the multifactorial nature of T2DM, its pathogenesis is still poorly understood (3). This disease is a metabolic disorder resulting from hyperglycemia and subsequent insulin resistance (IR) (4). Although genetics play a crucial role in contributing T2DM, the main Predisposing factors, including overeating, a sedentary lifestyle and ageing, are environmental (5, 6).

Patients with T2DM often develop hypertension and dyslipidemia, which bring up macrovascular complications (e.g., congestive heart failure) (7). In addition, chronic hyperglycemia in T2DM gives rise to microvascular complications, including nephropathy, neuropathy, and retinopathy, which ultimately lead to renal failure, muscle weakness, and visual impairment, respectively (7-9).

The colon modulates glucose metabolism through various mechanisms (10-14). It secretes cholecystokinin, affecting β cell proliferation and insulin secretion (15-17). It also affects glucose metabolism through its microbiota (18).

Gram-negative bacteria possess a factor called lipopolysaccharide (LPS) on their outer membrane. LPS can cause inflammation and aggravates metabolic disorders such as T2DM (18).

In addition, the gut microbiota (GM) produces several metabolites such as short-chain fatty acids (SCFA). SCFAs induces the secretion of glucagon-like peptide-1 (GLP-1), leading to insulin release (19). Therefore, partial or total resection of the colon, which is called "colectomy", can have extensive impact on the glucose metabolism. Colectomy is performed through open or laparoscopic surgery for treating several colon diseases such as familial adenomatous polyposis, Crohn's disease, ulcerative colitis, and colon cancer (Figure 1) (20, 21) (22).

Studies have shown that pre-existing T2DM influences the outcome of various surgical procedures (23). T2DM has been associated with an increased risk of complications such as surgical site infection following colectomy (24). Mortality rates have also been higher among T2DM patients undergoing colectomy (25).

Furthermore, some evidence suggests an increased risk of T2DM following colectomy (26). However, some studies have failed to show this association (27). Thus, the relationship between diabetes and colectomy is still unclear. This review aims to highlight the association between colectomy and T2DM and its related clinical data, which leads to a better understanding of their connection.

## Cholecystokinin

Cholecystokinin (CCK) is a gut hormone produced in the small and large bowel, significantly contributing to glucose regulation. There are two main receptors for CCK, including cholecystokinin A receptor (CCKAR, also known as CCK1R) and cholecystokinin B receptor (CCKBR, also known as CCK2R). CCKBR mediates the impacts of CCK on glucose homeostasis in the pancreas. It has been shown that CCK stimulates glucagon release from human pancreatic Langerhans islets in vitro. In rodents, CCK stimulates insulin secretion in a glucose-dependent manner.

Moreover, infusion of CCK-8, which contains eight amino acids, increases insulin concentration in the plasma and reduces glucose excursion after ingesting meals in healthy and T2DM subjects (15, 16). CCK also exerts proliferative effects on the β cells of the pancreas (28). Rushakoff et al. have shown that meal-induced elevation in CCK levels is higher in control subjects than diabetics. This suggests that T2DM is linked to impaired secretion of CCK (17).

## Gut microbiota in metabolism and glucose homeostasis

The GM is a collection of microorganisms in the gastrointestinal (GI) tract. Bacteroides and firmicutes are the most common phyla in human GM (29). The GM contributes in glucose homeostasis, metabolism of carbohydrates, production of several metabolites (e.g., SCFAs), bile acid metabolism, maintaining intestinal barrier integrity, and immune system maturation (30). Factors such as dietary patterns, medications, and mode of delivery (cesarean or vaginal) can influence the composition of GM (Figure 1) (31, 32).

Disruption of the GM composition is called "dysbiosis" (31). Recently, the role of dysbiosis in the development of metabolic disorders such as obesity, IR, and type 1 and type 2 diabetes has gained attention (11). The composition of GM in patients with metabolic disorders like T2DM is different from healthy individuals (33). Moreover, changes in the GM content are related to IR development in humans and animals (34-36).

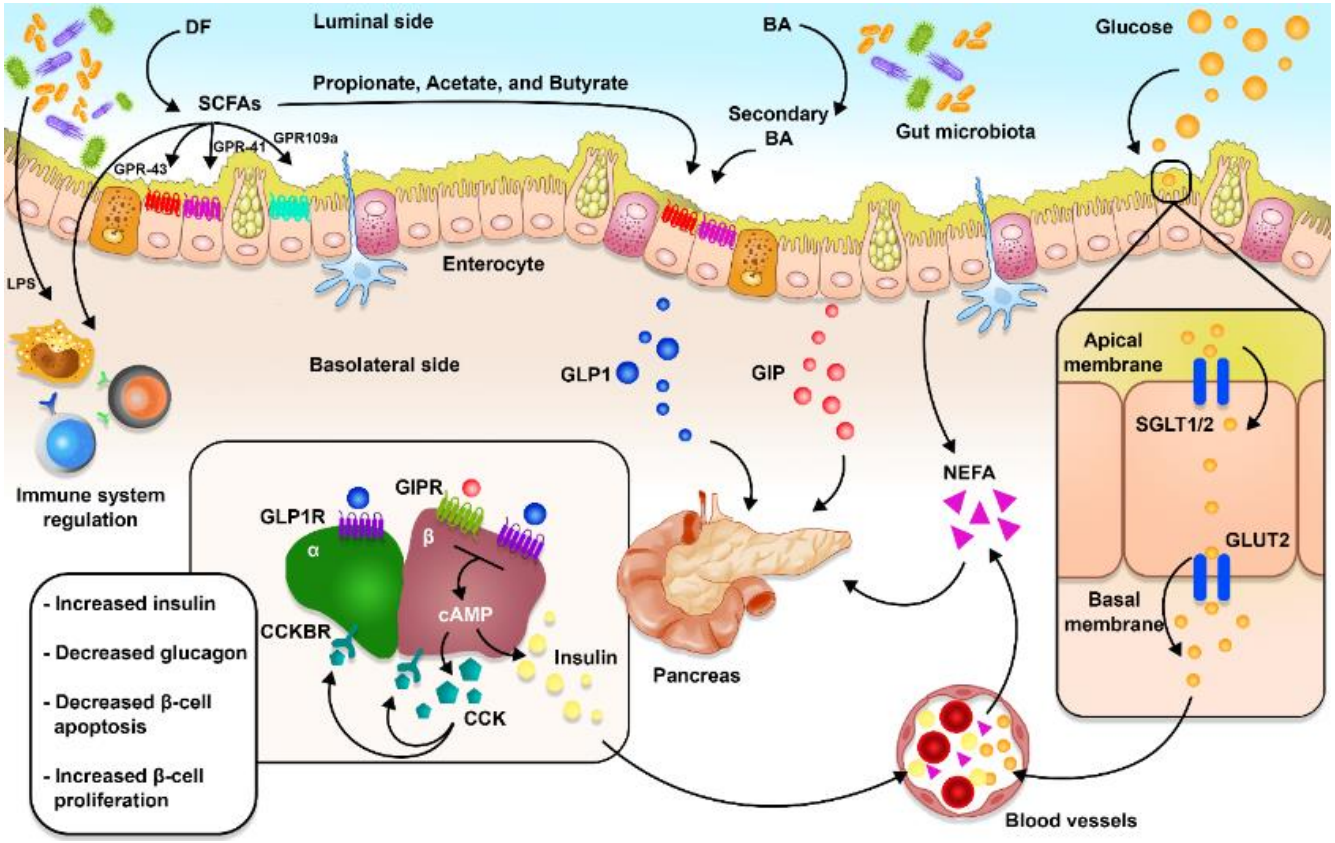


***Figure 1. How gut microbiota (GM) composition affects metabolism and glucose homeostasis:*** *a) Lipopolysaccharide (LPS) once translocated from the gut to the blood attaches to toll like receptor 4 and initiates inflammatory reactions related to the development of obesity and diabetes mellitus. GM prevents this by producing metabolites such as short chain fatty acids (SCFAs) that help maintain intestinal barrier integrity. b) GM plays an important role in bile acid (BA) metabolism and maintaining BA pool size/composition. Total serum BA affects the takeda G protein-coupled receptor 5 (TGR-5) receptors on intestinal cells stimulating glucagon-like peptide-1 (GLP-1) hormone secretion. GLP-1 along with peptide tyrosine tyrosine (PYY) and leptin stimulate insulin secretion and satiety following food intake. Therefore, a decrease in GLP-1 (and PYY) can be linked to obesity and high serum glucose levels. c) GM metabolizes dietary fibers (DF) into SCFAs. SCFAs (in addition to preserving intestinal barrier integrity) activate GPR43 and GPR41 receptors on intestinal cells, leading to the secretion of GLP-1 and PYY hormones.*

Although a growing body of literature has investigated the relationship between dysbiosis and metabolic disorders, its exact mechanism is still uncertain (37). Some mechanisms by which dysbiosis can promote metabolic disorders include alterations in LPS levels, intestinal barrier integrity, metabolite levels, BA metabolism, and gut hormone secretion (11, 29, 38, 39).

## Alterations in LPS levels

LPS, mostly known as endotoxin, is a significant constituent of the outer membrane of gram-negative bacteria (18). It attaches to toll-like receptor 4 (TLR-4) and initiates inflammatory reactions (18). Metabolic disorders such as obesity and T2DM have been linked to chronic low-grade inflammation, which might be partially due to the translocation of LPS from the gut to the blood (12, 13).

Reports have suggested that a high-fat diet in mice causes dysbiosis by increasing the number of gram-negative bacteria, leading to elevated LPS levels and low-grade inflammation (12, 40). Additionally, in humans, high levels of circulating LPS due to the absorption of endotoxins from the gut (i.e., metabolic endotoxemia) have been associated with T2DM (41). Higher LPS levels in patients with T1DM or T2DM have also been evidenced (42, 43).

In addition, GM produces several metabolites, such as SCFA, which are beneficial to the health of epithelial cells and the normal gut barrier (44). Thus, GM maintains intestinal barrier integrity and prevents harmful components like LPS from translocating into the blood (44). Dysbiosis gives rise to the impairment of the intestinal barrier or "leaky gut," which is another factor that causes high levels of LPS or metabolic endotoxemia in T2DM patients (45, 46). In one study, six months of exercise resulted in changes in gut composition, which improved intestinal barrier function in patients with T2DM (47).

## Alterations in bile acid metabolism

Bile acid (BA) is synthesized by hepatic cells from cholesterol and assists digestion and absorption of dietary lipids (48). GM is responsible for maintaining BA pool size, composition, and metabolism, by transforming it into secondary BA, consisting of deoxycholic acid and lithocholic acid (49, 50). Recently, evidence has indicated BA's signaling function by attaching to farnesoid X receptor and Takeda G protein-coupled receptor 5 (TGR-5) (51). These two receptors, expressed mainly on hepatocytes, play a key role in BA, fatty acids, and carbohydrate metabolism (51). Total serum BA also impacts post-prandial glucose levels by acting on TGR-5 receptors on enteroendocrine cells and stimulating GLP-1 secretion (52).

Interestingly, a human study showed altered GM and decreased levels of BA in fecal samples of T2DM patients (50). Furthermore, studies have shown antimicrobial properties for BA by destructing bacterial cell membranes and preventing bacterial overgrowth (48, 53). A high-fat diet can alter GM, resulting in a high number of bile-resistant bacteria, and bacterial overgrowth in the gut (48).

## Alterations in gut hormone secretion

The GI tract plays a crucial role in lipids and carbohydrates metabolism, appetite, and digestion by secreting hormones such as GLP-1, leptin, ghrelin, and PYY (11). GLP-1, PYY and leptin are also associated with insulin secretion and satiety. Hence, decreased levels of GLP-1 and PYY might be linked to obesity and high serum glucose level (54). Studies have revealed that GM regulates GI hormone secretion (55). GM metabolizes otherwise non-digestible dietary fibers (DF) into SCFA (50). SCFAs, mostly consisting of butyrate, acetate, and propionate, are the main metabolites produced in the large intestine(56). SCFAs are influential in the gut and host metabolism (57). They activate the G-protein coupled cell receptor 43 (GPR-43) and 41 (GPR-41) (58), also known as free fatty acid receptor 2 (FFAR-2) and 3 (FFAR-3) (59), which are involved in the regulation of lipid and glucose metabolism. These receptors are on the enteroendocrine L-cells in the colon. Their activation results in the secretion of peptide tyrosine (PYY) and GLP-1, which are gut-derived satiety hormones (60). Additionally, SCFA affects the metabolism and function of peripheral tissue and organs. As a result, SCFA contributes to the hemostasis in glucose and lipid metabolism (57).

It is well known that increased SCFA production has a great effect on immune and inflammatory function in the colon, mainly through influencing the mucosal secretion of IgA (61) and generating regulatory T cells (Treg) (62, 63). Beyond their side of production, SCFAs can influence immune and inflammatory responses in peripheral tissues (61, 64, 65). Supplementing naïve T cell cultures with propionate increases Treg development and lowers the expansion of inflammatory Th17 cells (65). Long-term colonic propionate delivery improves glucose homeostasis by suppressing low-grade systemic inflammation that accompanies obesity (66). IL-8 is a chemokine that induces migration of macrophages and neutrophils to sites of inflammation. It contributes to the proinflammatory properties of metabolic syndrome. This chemotaxis can impact processes that impede insulin signaling (67, 68). Studies have associated high levels of IL-8 with elevated IR in humans (68, 69). Propionate suppresses IL-8 expression (70). A randomized control trial showed that in T2DM patients, consumption of DF increased SCFA-producing bacteria, which lowered the hemoglobin A1C levels in the participants by increasing GLP-1 levels (19).

Dietary fibers intake regulates the activity and composition of the GM (71). Increasing the intake of DF has been associated with increased production of SCFA acetate, butyrate, and propionate, which improve insulin sensitivity in the whole body (72, 73). It has been suggested that SCFAs affect receptor-mediated mechanisms and metabolic pathways in numerous organs and tissue sites (60). In-vitro studies have suggested that FFAR-2 is expressed in human islets, and as mentioned previously, SCFAs function as ligands for GPR, FFAR3, FFAR2, and GPR109a. Propionate-mediated signaling enhances glucose-stimulated insulin release and protects β cells from apoptotic stimuli (74, 75).

## Fecal microbiota transplant in metabolic disorders

Recent evidence suggests that GM of patients with metabolic disorders differs from healthy individuals (14). Attempts have been made to modify these patients' GM by implementing fecal microbiota transplant (FMT) (14). Previously, this method had been used to treat patients with Clostridium difficile infection (76). In this technique, the fecal microbiota of a healthy individual is transplanted into the patient's gut (33). In an animal study, FMT improved IR in diabetic mice, which might be a promising treatment for T2DM (33).

In a randomized control trial, patients with new-onset T1DM received FMT, which halted the decline in insulin secretion and disease progression (77). A group of studies has shown that subjecting mice to a gut microbial transplant improves glycemic control and body composition by promoting the production of cecal propionate (78, 79).

## Colectomy

Colectomy is the surgical removal of the colon (20). Based on the resected segment, colectomy is divided into total, subtotal, right or left hemicolectomy, proctocolectomy, and segmental colectomy (80, 81). Laparoscopic and open surgery are the two main methods of colectomy (82). Rectal/colon cancer, diverticular disease, trauma, and inflammatory bowel disease (such as ulcerative colitis and Crohn's Disease) are some of the indications of colectomy (20, 82).

## Clinical findings

Colon cancer is one of the most common cancers diagnosed in the United States and worldwide, with a poor prognosis and a high risk of recurrence. Colectomy has been an effective treatment for colon cancer for many years. Nevertheless, this invasive treatment has been associated with some complications, which can be minimized by the identification of the underlying factors.

Diabetes, which affects about 9.3 percent of the global population (83), has been recognized as a contributing factor to the poor prognosis of various types of surgeries and other invasive treatments (23). It has been proven that different types of stress can disrupt insulin secretion and the hyperglycemic status of a diabetic patient by impairing some hormonal mechanisms and cytokine pathways. Thus, the risk of infection, other post-operative complications, and homeostatic disturbances, increase (84-87).

On the other hand, T2DM patients with high post-prandial glucose levels have abnormal intestinal normal flora (INF). It is not clear whether T2DM contributes to the formation of this combination of INF or whether the presence of this type of microbiota itself is a predisposing factor for diabetes. To date, however, few studies have been conducted on the relationship between colectomy and the risk of T2DM. In a retrospective study, Jackson et al. investigated the association of hyperglycemia with general surgery consequences among 9,638 surgeries. They found that mortality was higher among diabetic or pre-diabetic patients undergoing colectomy than in non-diabetic patients, with the leading cause of death among all patients being myocardial infarction (25).

A descriptive analysis of data from 169,325 patients by Ramsey et al. revealed that patients with insulin-dependent diabetes mellitus and, to a lesser extent, patients with non-insulin-dependent diabetes mellitus were more likely to have an adverse clinical outcome after colectomy than the control population. Most complications among diabetic patients encompassed post-operative infections (sepsis, pneumonia, and urinary tract infections), readmission, and reoperation (24).

A study evaluating the effect of comorbid diabetes on the short-term complications following colectomy showed that uncomplicated diabetes mellitus reduces the post-operative mortality compared to the control as well as the risk of post-operative complications. In contrast, patients with diabetes mellitus accompanied by other complications such as hypertension have worse outcomes than the control population (88).

In a meta-analysis of the data of a total number of 666,886 patients, Tan et al. found that colorectal surgery in patients with diabetes mellitus was associated with a higher risk of complications such as surgical site infections (SSI), anastomotic leak, urinary problems, and readmission. At the same time, there was no significant increase in risk for other complications such as sepsis, reoperation, and in-hospital mortality (89).

On the contrary, a retrospective cohort study that included 218,534 patients reported that patients with diabetes have a reduced mortality rate and fewer side effects after colectomy than non-diabetics. However, they did not observe a significant protective effect of diabetes on colorectal cancer surgery in uninsured or younger patients (90).

Ziegler and colleagues showed that although diabetes does not affect the development of an anastomotic leak, in people with diabetes who had an anastomotic leak, the mortality rate increases up to 4 times following colectomy compared to the population without diabetes. However, they also emphasize that in non-diabetic patients, hyperglycemia may be associated with an increased risk of post-operative mortality (91).

In another study on 533 cases of colorectal cancer, Flynn et al. showed that some comorbidities like T2DM are not related to severe post-operative complications following colectomy (92).

Examining 46,279 colectomy cases showed that some patients undergoing colectomy had an increased risk of T2DM compared to patients undergoing other surgeries. Of note, this observation was more significant among people who underwent surgery on the left side of the colon. Although they acknowledged insufficient evidence, they also claimed that a colectomy of the left side of the colon could be considered influential in enhancing the risk of developing T2DM (26).

Recently, in a population-based cohort analysis (on a total number of 642 patients), Wu et al. showed that Colectomy (mainly transverse and right colon colectomy) in non-cancerous patients could be considered efficacious in reducing the risk of developing T2DM (27).

However, few studies have been conducted on the relationship between colectomy and either pre- or post-operative T2DM, and existing data are inconclusive due to a lack of sample size and information consistency in different study outcomes (Table 1). Nonetheless, given the evidence, there may be a possible link between diabetes and colectomy post-operative complications, which requires more extensive and detailed controlled research to prove this possibility.

## Conclusion

Diabetes is a significant health problem, and its incidence is dramatically increasing. Some studies suggest an increased risk of T2DM following colectomy. This might be associated with altered GM and changes in gut hormone secretion. Additionally, the association between diabetes and different types of colectomies needs to be validated. A cohort study concluded that the risk of T2DM decreases primarily with right hemicolectomy or transverse colectomy. This might suggest that the composition of GM is not homogenous throughout the colon. Thus, the data on the relationship between T2DM and Colectomy is inadequate, and more work is needed to establish any assumptions.

*Table 1. Studies that have shown the association between colectomy and type 2 diabetes.*

| Author/ year (ref) | Type of study | Number and type of patients and controls | Type of the surgery | Results | Outcomes |
|---|---|---|---|---|---|
| **Wu et al. 2021 (27)** | Retrospective cohort | **Case:** 642 patients that underwent colectomy for non-cancerous causes **Control:** 2568 patients without colectomy | Laparoscopic or Laparotomic colectomy | There is a negative association between colectomy and the risk type 2 diabetes. | The patients underwent colectomy, particularly right or transverse colectomy, had decreased risk for developing type 2 diabetes. |
| **Jensen et al. 2018 (26)** | Retrospective cohort | **Case:** 46279 patients that underwent colectomy **Control:** 694110 patients who underwent other surgeries | Laparotomic colectomy | There is a positive association between colectomy and the risk type 2 diabetes. | The risk of type 2 diabetes increased after colectomy, particularly left hemicolectomy. |
| **Punchai et al. 2020 (93)** | Cross-sectional | 171 patients with type 2 diabetes who underwent colectomy for benign diseases | Laparoscopic or Laparotomic colectomy | There is no significant association between colectomy and diabetes | Colectomy is not associated with long-term changes in body weight or glycemic control. |

## Declaration

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The authors declare no conflict of interest.

**Authors' contributions**
A.T. made the initial draft. S.O.T., N.S.F.G., S.P. and A.K. edited the initial draft. Z.K., K.K.A., S.F.S.N., K.M. and M.V. edited the manuscript and approved the final version.

**Ethics approval**
Not applicable.

## References

1. Lee JM, Okumura MJ, Freed GL, Menon RK, Davis MM. Trends in hospitalizations for diabetes among children and young adults: United States, 1993–2004. Diabetes care. 2007;30(12):3035-9.

2. Reed J, Bain S, Kanamarlapudi V. A review of current trends with Type 2 diabetes epidemiology, aetiology, pathogenesis, treatments and future perspectives. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy. 2021;14:3567.

3. Stumvoll M, Goldstein BJ, Van Haeften TW. Type 2 diabetes: principles of pathogenesis and therapy. The Lancet. 2005;365(9467):1333-46.

4. Serbis A, Giapros V, Kotanidou EP, Galli-Tsinopoulou A, Siomou E. Diagnosis, treatment and prevention of type 2 diabetes mellitus in children and adolescents. World Journal of Diabetes. 2021;12(4):344.

5. Robertson RP, Bogardus C. Antagonist: diabetes and insulin resistance: philosophy, science, and the multiplier hypothesis. Discussion. The Journal of laboratory and clinical medicine. 1995;125(5):560-5.

6. Li Y, Xu W, Liao Z, Yao B, Chen X, Huang Z, et al. Induction of long-term glycemic control in newly diagnosed type 2 diabetic patients is associated with improvement of β-cell function. Diabetes care. 2004;27(11):2597-602.

7. Pinhas-Hamiel O, Zeitler P. Acute and chronic complications of type 2 diabetes mellitus in children and adolescents. The Lancet. 2007;369(9575):1823-31.

8. Copeland KC, Zeitler P, Geffner M, Guandalini C, Higgins J, Hirst K, et al. Characteristics of adolescents and youth with recent-onset type 2 diabetes: the TODAY cohort at baseline. The Journal of Clinical Endocrinology & Metabolism. 2011;96(1):159-67.

9. Group TS. A clinical trial to maintain glycemic control in youth with type 2 diabetes. New England Journal of Medicine. 2012;366(24):2247-56.

10. Drozdowski L, Thomson AB. Intestinal hormones and growth factors: effects on the small intestine. World journal of gastroenterology: WJG. 2009;15(4):385.

11. Lupien-Meilleur J, Andrich DE, Quinn S, Micaelli-Baret C, St-Amand R, Roy D, et al. Interplay Between Gut Microbiota and Gastrointestinal Peptides: Potential Outcomes on the Regulation of Glucose Control. Can J Diabetes. 2020;44(4):359-67.

12. Fuke N, Nagata N, Suganuma H, Ota T. Regulation of Gut Microbiota and Metabolic Endotoxemia with Dietary Factors. Nutrients. 2019;11(10).

13. Ebrahimzadeh Leylabadlo H, Sanaie S, Sadeghpour Heravi F, Ahmadian Z, Ghotaslou R. From role of gut microbiota to microbial-based therapies in type 2-diabetes. Infect Genet Evol. 2020;81:104268.

14. Browne AS, Kelly CR. Fecal Transplant in Inflammatory Bowel Disease. Gastroenterology clinics of North America. 2017;46(4):825-37.

15. Drucker DJ. The role of gut hormones in glucose homeostasis. The Journal of clinical investigation. 2007;117(1):24-32.

16. Ahren B, Holst JJ, Efendic S. Antidiabetogenic action of cholecystokinin-8 in type 2 diabetes. The Journal of Clinical Endocrinology & Metabolism. 2000;85(3):1043-8.

17. Rushakoff RA, Goldfine I, Beccaria LJ, Mathur A, Brand RJ, Liddle RA. Reduced postprandial cholecystokinin (CCK) secretion in patients with noninsulin-dependent diabetes mellitus: evidence for a role for CCK in regulating postprandial hyperglycemia. The Journal of Clinical Endocrinology & Metabolism. 1993;76(2):489-93.

18. Ballan R, Saad SMI. Characteristics of the Gut Microbiota and Potential Effects of Probiotic Supplements in Individuals with Type 2 Diabetes mellitus. Foods. 2021;10(11).

19. Zhao L, Zhang F, Ding X, Wu G, Lam YY, Wang X, Fu H, Xue X, Lu C, Ma J, Yu L. Gut bacteria selectively promoted by dietary fibers alleviate type 2 diabetes. Science. 2018 Mar 9;359(6380):1151-6.

20. Chang GJ, Nelson H. Laparoscopic colectomy. Current gastroenterology reports. 2005;7(5):396-403.

21. Impact of postoperative non-steroidal anti-inflammatory drugs on adverse events after gastrointestinal surgery. The British journal of surgery. 2014;101(11):1413-23.

22. Cotte E, Mohamed F, Nancey S, François Y, Glehen O, Flourié B, et al. Laparoscopic total colectomy: Does the indication influence the outcome? World journal of gastrointestinal surgery. 2011;3(11):177-82.

23. Pozzilli P, Leslie R. Infections and diabetes: mechanisms and prospects for prevention. Diabetic Medicine. 1994;11(10):935-41.

24. Ramsey T GSaNF. Postoperative Complications of Colectomy in Diabetes Patients. Austin J Surg. 2017;4(4).

25. Jackson RS, Amdur RL, White JC, Macsata RA. Hyperglycemia is associated with increased risk of morbidity and mortality after colectomy for cancer. Journal of the American College of Surgeons. 2012;214(1):68-80.

26. Jensen AB, Sørensen TI, Pedersen O, Jess T, Brunak S, Allin KH. Increase in clinically recorded type 2 diabetes after colectomy. Elife. 2018;7:e37420.

27. Wu C-C, Lee C-H, Hsu T-W, Yeh C-C, Lin M-C, Chang C-M, et al. Is colectomy associated with the risk of type 2 diabetes in patients without colorectal cancer? A population-based cohort study. Journal of clinical medicine. 2021;10(22):5313.

28. Kuntz E, Pinget M, Damgé P. Cholecystokinin octapeptide: a potential growth factor for pancreatic beta cells in diabetic rats. Jop. 2004;5(6):464-75.

29. Lee CJ, Sears CL, Maruthur N. Gut microbiome and its role in obesity and insulin resistance. Ann N Y Acad Sci. 2020;1461(1):37-52.

30. Zhang YJ, Li S, Gan RY, Zhou T, Xu DP, Li HB. Impacts of gut bacteria on human health and diseases. Int J Mol Sci. 2015;16(4):7493-519.

31. Nuli R, Cai J, Kadeer A, Zhang Y, Mohemaiti P. Integrative Analysis Toward Different Glucose Tolerance-Related Gut Microbiota and Diet. Front Endocrinol (Lausanne). 2019;10:295.

32. Reyman M, van Houten MA, van Baarle D, Bosch A, Man WH, Chu M, et al. Impact of delivery mode-associated gut microbiota dynamics on health in the first year of life. Nat Commun. 2019;10(1):4997.

33. Wang H, Lu Y, Yan Y, Tian S, Zheng D, Leng D, et al. Promising Treatment for Type 2 Diabetes: Fecal Microbiota Transplantation Reverses Insulin Resistance and Impaired Islets. Front Cell Infect Microbiol. 2019;9:455.

34. Everard A, Belzer C, Geurts L, Ouwerkerk JP, Druart C, Bindels LB, et al. Cross-talk between Akkermansia muciniphila and intestinal epithelium controls diet-induced obesity. Proceedings of the national academy of sciences. 2013;110(22):9066-71.

35. Everard A, Cani PD. Diabetes, obesity and gut microbiota. Best practice & research Clinical gastroenterology. 2013;27(1):73-83.

36. Larsen N, Vogensen FK, Van Den Berg FW, Nielsen DS, Andreasen AS, Pedersen BK, et al. Gut microbiota in human adults with type 2 diabetes differs from non-diabetic adults. PloS one. 2010;5(2):e9085.

37. Utzschneider KM, Kratz M, Damman CJ, Hullar M. Mechanisms Linking the Gut Microbiome and Glucose Metabolism. J Clin Endocrinol Metab. 2016;101(4):1445-54.

38. Adachi K, Sugiyama T, Yamaguchi Y, Tamura Y, Izawa S, Hijikata Y, Ebi M, Funaki Y, Ogasawara N, Goto C, Sasaki M. Gut microbiota disorders cause type 2 diabetes mellitus and homeostatic disturbances in gut-related metabolism in Japanese subjects. Journal of clinical biochemistry and nutrition. 2019;64(3):231-8.

39. Sharma S, Tripathi P. Gut microbiome and type 2 diabetes: where we are and where to go? J Nutr Biochem. 2019;63:101-8.

40. Aydin Ö, Nieuwdorp M, Gerdes V. The Gut Microbiome as a Target for the Treatment of Type 2 Diabetes. Current Diabetes Reports. 2018;18(8).

41. Pussinen PJ, Havulinna AS, Lehto M, Sundvall J, Salomaa V. Endotoxemia is associated with an increased risk of incident diabetes. Diabetes Care. 2011;34(2):392-7.

42. Devaraj S, Dasu MR, Park SH, Jialal I. Increased levels of ligands of Toll-like receptors 2 and 4 in type 1 diabetes. Diabetologia. 2009;52(8):1665-8.

43. Creely SJ, McTernan PG, Kusminski CM, Fisher f M, Da Silva NF, Khanolkar M, et al. Lipopolysaccharide activates an innate immune system response in human adipose tissue in obesity and type 2 diabetes. Am J Physiol Endocrinol Metab. 2007;292(3):E740-7.

44. Usuda H, Okamoto T, Wada K. Leaky Gut: Effect of Dietary Fiber and Fats on Microbiome and Intestinal Barrier. Int J Mol Sci. 2021;22(14).

45. Chakaroun RM, Massier L, Kovacs P. Gut Microbiome, Intestinal Permeability, and Tissue Bacteria in Metabolic Disease: Perpetrators or Bystanders? Nutrients. 2020;12(4).

46. de Kort S, Keszthelyi D, Masclee AA. Leaky gut and diabetes mellitus: what is the link? Obes Rev. 2011;12(6):449-58.

47. Pasini E, Corsetti G, Assanelli D, Testa C, Romano C, Dioguardi FS, et al. Effects of chronic exercise on gut microbiota and intestinal barrier in human with type 2 diabetes. Minerva Med. 2019;110(1):3-11.

48. Ramírez-Pérez O, Cruz-Ramón V, Chinchilla-López P, Méndez-Sánchez N. The Role of the Gut Microbiota in Bile Acid Metabolism. Annals of Hepatology. 2017;16:S21-S6.

49. Staley C, Weingarden AR, Khoruts A, Sadowsky MJ. Interaction of gut microbiota with bile acid metabolism and its influence on disease states. Appl Microbiol Biotechnol. 2017;101(1):47-64.

50. Zhao L, Lou H, Peng Y, Chen S, Fan L, Li X. Elevated levels of circulating short-chain fatty acids and bile acids in type 2 diabetes are linked to gut barrier disruption and disordered gut microbiota. Diabetes Res Clin Pract. 2020;169:108418.

51. Cariou B, van Harmelen K, Duran-Sandoval D, van Dijk TH, Grefhorst A, Abdelkarim M, et al. The farnesoid X receptor modulates adiposity and peripheral insulin sensitivity in mice. J Biol Chem. 2006;281(16):11039-49.

52. Malin SK, Kashyap SR. Effects of various gastrointestinal procedures on beta-cell function in obesity and type 2 diabetes. Surg Obes Relat Dis. 2016;12(6):1213-9.

53. Kurdi P, Kawanishi K, Mizutani K, Yokota A. Mechanism of growth inhibition by free bile acids in lactobacilli and bifidobacteria. J Bacteriol. 2006;188(5):1979-86.

54. Holst JJ. The physiology of glucagon-like peptide 1. Physiological reviews. 2007;87(4):1409-39.

55. Zhao L, Lou H, Peng Y, Chen S, Zhang Y, Li X. Comprehensive relationships between gut microbiome and faecal metabolome in individuals with type 2 diabetes and its complications. Endocrine. 2019;66(3):526-37.

56. Pascale A, Marchesi N, Marelli C, Coppola A, Luzi L, Govoni S, et al. Microbiota and metabolic diseases. Endocrine. 2018;61(3):357-71.

57. Boets E, Gomand SV, Deroover L, Preston T, Vermeulen K, De Preter V, et al. Systemic availability and metabolism of colonic-derived short-chain fatty acids in healthy subjects: a stable isotope study. The Journal of physiology. 2017;595(2):541-55.

58. Brown AJ, Goldsworthy SM, Barnes AA, Eilert MM, Tcheang L, Daniels D, et al. The Orphan G protein-coupled receptors GPR41 and GPR43 are activated by propionate and other short chain carboxylic acids. Journal of Biological Chemistry. 2003;278(13):11312-9.

59. Den Besten G, Van Eunen K, Groen AK, Venema K, Reijngoud D-J, Bakker BM. The role of short-chain fatty acids in the interplay between diet, gut microbiota, and host energy metabolism. Journal of lipid research. 2013;54(9):2325-40.

60. González Hernández MA, Canfora EE, Jocken JW, Blaak EE. The short-chain fatty acid acetate in body weight control and insulin sensitivity. Nutrients. 2019;11(8):1943.

61. Kim M, Qie Y, Park J, Kim CH. Gut microbial metabolites fuel host antibody responses. Cell host & microbe. 2016;20(2):202-14.

62. Arpaia N, Campbell C, Fan X, Dikiy S, Van Der Veeken J, Deroos P, et al. Metabolites produced by commensal bacteria promote peripheral regulatory T-cell generation. Nature. 2013;504(7480):451-5.

63. Smith PM, Howitt MR, Panikov N, Michaud M, Gallini CA, Bohlooly-y M, et al. The microbial metabolites, short-chain fatty acids, regulate colonic Treg cell homeostasis. Science. 2013;341(6145):569-73.

64. Trompette A, Gollwitzer ES, Yadava K, Sichelstiel AK, Sprenger N, Ngom-Bru C, et al. Gut microbiota metabolism of dietary fiber influences allergic airway disease and hematopoiesis. Nature medicine. 2014;20(2):159-66.

65. Haghikia A, Jörg S, Duscha A, Berg J, Manzel A, Waschbisch A, et al. Dietary fatty acids directly impact central nervous system autoimmunity via the small intestine. Immunity. 2015;43(4):817-29.

66. Chambers ES, Byrne CS, Morrison DJ, Murphy KG, Preston T, Tedford C, et al. Dietary supplementation with inulin-propionate ester or inulin improves insulin sensitivity in adults with overweight and obesity with distinct effects on the gut microbiota, plasma metabolome and systemic inflammatory responses: a randomised cross-over trial. Gut. 2019;68(8):1430-8.

67. McNelis JC, Olefsky JM. Macrophages, immunity, and metabolic disease. Immunity. 2014;41(1):36-48.

68. Kim C, Park H, Kawada T, Kim JH, Lim D, Hubbard N, et al. Circulating levels of MCP-1 and IL-8 are elevated in human obese subjects and associated with obesity-related parameters. International journal of obesity. 2006;30(9):1347-55.

69. Herder C, Haastert B, Muller-Scholze S, Koenig W, Thorand B, Holle R, et al. Association of systemic chemokine concentrations with impaired glucose tolerance and type 2 diabetes: results from the Cooperative Health Research in the Region of Augsburg Survey S4 (KORA S4). Diabetes. 2005;54(suppl_2):S11-S7.

70. Hung TV, Suzuki T. Short-chain fatty acids suppress inflammatory reactions in Caco-2 cells and mouse colons. Journal of agricultural and food chemistry. 2018;66(1):108-17.

71. David LA, Maurice CF, Carmody RN, Gootenberg DB, Button JE, Wolfe BE, et al. Diet rapidly and reproducibly alters the human gut microbiome. Nature. 2014;505(7484):559-63.

72. Macfarlane S, Macfarlane GT. Regulation of short-chain fatty acid production. Proceedings of the Nutrition Society. 2003;62(1):67-72.

73. Flint HJ, Scott KP, Duncan SH, Louis P, Forano E. Microbial degradation of complex carbohydrates in the gut. Gut microbes. 2012;3(4):289-306.

74. Tan J, McKenzie C, Potamitis M, Thorburn AN, Mackay CR, Macia L. The role of short-chain fatty acids in health and disease. Advances in immunology. 2014;121:91-119.

75. Pingitore A, Chambers ES, Hill T, Maldonado IR, Liu B, Bewick G, et al. The diet-derived short chain fatty acid propionate improves beta-cell function in humans and stimulates insulin secretion from human islets in vitro. Diabetes, Obesity and Metabolism. 2017;19(2):257-65.

76. Weingarden AR, Vaughn BP. Intestinal microbiota, fecal microbiota transplantation, and inflammatory bowel disease. Gut Microbes. 2017;8(3):238-52.

77. De Groot P, Nikolic T, Pellegrini S, Sordi V, Imangaliyev S, Rampanelli E, Hanssen N, Attaye I, Bakker G, Duinkerken G, Joosten A. Faecal microbiota transplantation halts progression of human new-onset type 1 diabetes in a randomised controlled trial. Gut. 2021 Jan 1;70(1):92-105.

78. Ridaura VK, Faith JJ, Rey FE, Cheng J, Duncan AE, Kau AL, et al. Gut microbiota from twins discordant for obesity modulate metabolism in mice. Science. 2013;341(6150).

79. Liou AP, Paziuk M, Luevano J-M, Machineni S, Turnbaugh PJ, Kaplan LM. Conserved shifts in the gut microbiota due to gastric bypass reduce host weight and adiposity. Science translational medicine. 2013;5(178):178ra41-ra41.

80. Böhm G, O'Dwyer ST. The fate of the rectal stump after subtotal colectomy for ulcerative colitis. International journal of colorectal disease. 2007;22(3):277-82.

81. Hopping JR, Bardakcioglu O. Single-port laparoscopic right hemicolectomy: intermediate results. JSLS : Journal of the Society of Laparoendoscopic Surgeons. 2013;17(1):5-8.

82. Fichtner-Feigl S. Biology-and Location-Oriented Precision Treatment of Rectal Cancer: Present and Future. Visceral medicine. 2020;36(5):381-7.

83. Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas. Diabetes research and clinical practice. 2019;157:107843.

84. Brem H, Tomic-Canic M. Cellular and molecular basis of wound healing in diabetes. The Journal of clinical investigation. 2007;117(5):1219-22.

85. Delamaire M, Maugendre D, Moreno M, Le Goff MC, Allannic H, Genetet B. Impaired leucocyte functions in diabetic patients. Diabetic Medicine. 1997;14(1):29-34.

86. Geerlings SE, Hoepelman AI. Immune dysfunction in patients with diabetes mellitus (DM). FEMS Immunology & Medical Microbiology. 1999;26(3-4):259-65.

87. Marhoffer W, Stein M, Maeser E, Federlin K. Impairment of polymorphonuclear leukocyte function and metabolic control of diabetes. Diabetes care. 1992;15(2):256-60.

88. Lee K-C, Chung K-C, Chen H-H, Cheng K-C, Wu K-L, Song L-C, et al. The Impact of Comorbid Diabetes on Short-Term Postoperative Outcomes in Stage I/II Colon Cancer Patients Undergoing Open Colectomy. BioMed Research International. 2020;2020.

89. Tan D, Yaow C, Mok H, Ng C, Tai C, Tham H, et al. The influence of diabetes on postoperative complications following colorectal surgery. Techniques in Coloproctology. 2021:1-12.

90. Anand N, Chong CA, Chong RY, Nguyen GC. Impact of diabetes on postoperative outcomes following colon cancer surgery. Journal of general internal medicine. 2010;25(8):809-13.

91. Ziegler MA, Catto JA, Riggs TW, Gates ER, Grodsky MB, Wasvary HJ. Risk factors for anastomotic leak and mortality in diabetic patients undergoing colectomy: analysis from a statewide surgical quality collaborative. Archives of Surgery. 2012;147(7):600-5.

92. Flynn DE, Mao D, Yerkovich ST, Franz R, Iswariah H, Hughes A, et al. The impact of comorbidities on post-operative complications following colorectal cancer surgery. PloS one. 2020;15(12):e0243995.

93. Punchai S, Wilson RL, Meister KM, Nor Hanipah Z, Vangoitsenhoven R, Schauer PR, et al. Does Colectomy Improve Type 2 Diabetes? Obes Surg. 2020;30(6):2429-33.

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