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Diabetic patients and postoperative complications in colorectal surgery

Ioana Paunica[1,2], Adrian Silaghi[3,4*], Daniela Gabriela Bălan[5], Bogdan Socea[3,6], Cristian Balalau[3,6], Florin Silviu Groseanu[7], George Alexandru Popescu[2], Dragos Epistatu[8], Vlad Denis Constantin[3,6]

[1] *Carol Davila University of Medicine and Pharmacy, N.C. Paulescu National Institute, Bucharest, Romania*
[2] *Carol Davila University of Medicine and Pharmacy, Doctoral School, Bucharest, Romania*
[3] *St. Pantelimon Emergency Clinical Hospital, Department of General Surgery, Bucharest, Romania*
[4] *Dunarea de Jos University, Faculty of Medicine and Pharmacy, Doctoral School, Galati, Romania*
[5] *Carol Davila University of Medicine and Pharmacy, Department of Physiology, Bucharest, Romania*
[6] *Carol Davila University of Medicine and Pharmacy, Department of General Surgery, Bucharest, Romania*
[7] *St. Pantelimon Emergency Clinical Hospital, Department of Orthopedics and Trauma-Surgery, Bucharest, Romania*
[8] *Carol Davila University of Medicine and Pharmacy, Department of Radiology, Bucharest, Romania*

ABSTRACT

Diabetes mellitus is one of the most common comorbidities of patients undergoing surgery. Colorectal surgery is frequently associated with postoperative complications, and diabetic patients represent a population that presents a high risk of developing such complications. Understanding the interrelationships between neoplastic disease and diabetes, as well as the pathophysiological mechanisms underlying postoperative complications, are essential for effective therapeutic management. Genetic predispositions, alterations in the gut microbiota, inflammatory response, ischemic, thrombotic and infectious processes contribute significantly to the development of severe surgical complications, such as anastomotic fistulas. Postoperative ileus, characterized by gastrointestinal dysmotility, is common in diabetic patients due to neuropathic dysfunction and altered intestinal metabolism. In addition, diabetic patients are at increased risk of intestinal ischemia, requiring specific perioperative care. The strategies to avoid these complications assume an adequate surgical technique, a personalized anesthesia management, and last but not least, the best possible glycemic control. This article highlights the importance of a better understanding of the interaction between diabetes and postoperative complications, in order to obtain good results with an important impact on the patient's health and well-being.

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***Corresponding author:**

Adrian Silaghi,

St. Pantelimon Emergency Clinical Hospital, Department of General Surgery, Bucharest, Romania

E-mail: adriansilaghi2014@gmail.com

Introduction

Diabetes mellitus is one of the most common comorbidities of operated patients, approximately 25% of them having elevated blood glucose levels [1]. The global prevalence of diabetes mellitus is increasing, estimates being that approximately 10.2% of the population will have raised glycemia in 2030 [2]. Diabetic patients generally present multiple risk factors, such as an increased risk of heart disease, a decrease in the immune response to various infectious pathogens (i.e. reduced opsonization of phagocytosis and chemotaxis), deficiencies in the area of microvascularization, etc. All this leads to the delay of the healing processes, thus resulting in an increased frequency of surgical complications, especially in the case of diseases with colorectal localization [3]. Another link between colon cancer and diabetes is supported by the presence of similar (genetic, environmental and bacterial) risk factors for the development of both pathological entities, often associating and reinforcing each other [4].

This article aims to identify suggestive data from the literature supporting common factors in the occurrence and evolution of colon cancer and diabetes mellitus, the main postoperative complications of colorectal surgery in patients with diabetes mellitus, and how such complications can be avoided, with the aim of obtaining the best possible results in terms of medical evolution, as well as patient compliance and well-being.

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Discussions

Diabetes mellitus and colonic cancer

Diabetes mellitus (DM) is a pathological condition characterized by the exposure of cells to high levels of blood glucose (in association with a chronic pro-inflammatory state), which leads to varying degrees of impairments of multiple systems and organs [5]. In type I diabetes, there is a decrease in insulin synthesis due to autoimmune destruction of pancreatic β-cells, while in type II diabetes, elevated blood glucose levels occur secondary to the association between increased tissue resistance to insulin and inadequate synthesis of insulin [6]. The development of diabetes often involves a combination of genetic and environmental factors. Therefore, a definite diagnosis of diabetes requires the determination of fasting blood glucose (a value above 126 mg/dL being suggestive), the determination of blood glucose 2 hours after a meal, or the determination of glycated hemoglobin. Values above 200 mg/dL for glucose and more than 6.5% for glycated hemoglobin are diagnostic for one of the two forms of diabetes [7].

Risk factors associated with the onset and exacerbation of type II diabetes may be common to those of colorectal cancer. Thus, obesity, smoking, decreased physical activity and a diet low in dietary fiber and rich in refined sugars can lead to the appearance of the two pathological entities in association [8]. In addition to the classic risk factors for the development of colorectal cancer and diabetes, it is assumed that the microbiota could influence both the onset and the evolution of these diseases [9]. Fusobacterium nucleatum, a bacterium that can be found in the flora of the colon, can mediate the response to immunotherapy or chemotherapy, being considered a negative prognostic factor in colorectal cancer [10]. In addition to this bacterial strain, there are also other infectious agents, all of which can be influenced by the administration of various foods and medications. Thus, the administration of Metformin leads to an increase in the variability of bacterial species in the colon microbiota, reducing the risk of colorectal cancer, especially in patients with type II diabetes mellitus [9]. Other neoplastic pathologies that may be associated with elevated blood glucose levels include breast, lung, liver, pancreatic, endometrial, or ovarian cancers (due to increased synthesis of estrogen hormones) and a protective factor by reducing testosterone concentration for prostate cancer [11].

Obesity is a risk factor for both colorectal cancer and diabetes, an association that is particularly seen in overweight men and women [12]. Thus, the expression of fatty acid synthase (FASN), cyclin-dependent kinase inhibitor 1B (CDKN1B) and CDKN1A are influenced by the amount of energy reaching the cell, factors that can influence the growth, differentiation and interaction of tumor cells with normal cells [13]. Another factor that could contribute to the onset of colorectal cancer in diabetic patients is the modification of the levels of sex hormones such as estradiol, sex hormone binding globulins, and adiponectin, leading to an increased incidence rate of neoplasia, especially in men. This factor is highlighted in an analysis of 408,931 patients, from countries with a high standard of living and a Western-style diet [5].

Pathogenesis of cancer and diabetes

Cellular glucose metabolism is mediated by receptor binding and activation of the AMP-activated protein kinase (AMPK) pathway [14], leading to activation of RAS, c-myc, glucose transporter 1 (GLUT1), and PI3K/AKT factors, which favor glucose influx in the cell. In conditions of chronic inflammation such as diabetes, obesity, neoplastic states, or atherosclerosis, all these pathways are activated/exacerbated. Especially in colorectal cancer, the GLUT1 pathway is overactivated which favors tissue growth in a mutagenic manner, being a negative prognostic factor for any histological type [6]. In type II diabetes mellitus, there is (secondary to elevated blood glucose levels) an overexpression of insulin receptors and of the IGF1-PI3K-AKT-mTor pathway [15], which stimulate the neoplastic cells via their surface receptors, thus promoting the development of malignant cells, invasion, and angiogenesis by VEGF gene aberrant expression [16].

Analyzing the genome of type II DM patients, there were alterations in the genes encoding transcription factor 7-like 2 (TCF7L2), tumor protein P53 inducible nuclear protein 1 (TP53INP1), calcium-/calmodulin-dependent protein kinase ID, and gremlin 1 (GREM1), some of which are also involved in the onset and development of colorectal cancer. The role of TCF7L2 is to suppress the invasion of normal cells by tumor cells; its mutations lead to an increased risk of malignancy by activating the WNT/B-cadherin pathway, resulting in cyclin D1 and c-Myc expression [17], as well as in the development of DM [18]. The presence of an altered TP53INP1 gene leads to the appearance of neoplastic cells, as their autophagy is reduced, demonstrated by its inhibition by miR-221 observed in metastatic colon cancer [5].

In colorectal cancer and diabetes, amplifications of oncogenes or inactivation of tumor suppressor genes can occur secondary to hypo- or hypermethylation. Septin 9 (SEPT9) methylation is a fairly sensitive and specific marker for colorectal cancer, reaching a sensitivity of 77.4% in metastatic cases [19]. DNA hypermethylation also occurs in type II diabetes at the SEPT9 and cyclin-dependent kinase inhibitor 1A (Cdkn1a) promoters, blocking the formation of new β-cell clones. Consequently, there is a global decrease in function, especially regarding insulin release under conditions of hyperglycemia, resulting in decreased glucose tolerance and subsequent type II diabetes [20].

Mir-16 is a protein involved in cell differentiation and proliferation processes, strongly suppressing angiogenesis and the transformation of mesenchymal cells into epithelial cells [21]. Through the miR-16-5p/ALDH1A3/PKM2 pathway, it is also involved in aerobic glucose metabolism, thus strongly impacting the suppression of pathological cell clones in colorectal cancer [22]. The association of diabetes with colorectal cancer through mir-16 implies a decrease in response to oncologic treatment, higher recurrence rates, and overall poorer prognosis when blood glucose levels exceed 110 mg/dL [23].

Postoperative complications in colorectal cancer

Surgical treatment of colon cancer has evolved, resulting in variability of methods regarding the stage and histological type of cancer. For early stages, minimally invasive approaches with endoscopic mucosal dissection are preferred [24], while in cases of submucosal involvement, resection of both the colon segment and its tributary lymph nodes is performed [25]. The approach can be minimally invasive using laparoscopy, robotic surgery, or conventional surgery, each with specific complication rates.

Postoperative adhesions formation

The formation of adhesions and the occurrence of small bowel obstruction are complications that occur especially in open surgery. They depend on several factors such as male sex, emergency surgery, exposure of small bowel loops to atmospheric air, bacterial contamination [26]. They are also influenced by elevated blood glucose levels that lead to chronic inflammation, oxidative stress and formation of fibrous tissue in various organs, accentuating pro-inflammatory and pro-oxidative elements at the tissue level due to the increased expression of molecules that promote fibrosis (TGF-β, etc.) [27]. Postoperative adhesion formation in patients with high blood glucose levels is favored by the higher expression of reactive oxygen species (ROS), which leads to formation of macromolecular complexes through interaction with proteins, lipids, or DNA chains, resulting thus in increased oxidative stress state [28]. In conditions of hyperglycemia, there is excessive pyruvate formation, subsequently leading to NADH formation, accumulation of superoxide ions at the mitochondrial level, and excessive production of proinflammatory cytokines and growth factors, interfering with normal tissue repair and favoring the formation of adhesions [29]. Advanced glycation end-product formation is another component of the increased oxidative stress state by excessive NADH formation and their interference with nuclear factor kappa B [30]. Secondary to this phenomenon, an increased expression of proinflammatory genes such as TNF-α and VCAM-1 are detected, which are key factors in the formation of new adhesions at the peritoneal level [31].

Management of patients with postoperative adhesions can be both operative and non-operative. The non operative management is characterized by the administration of prokinetic treatment, parenteral nutrition and digestive rest, but reintervention rates are significantly increased [27]. Laparoscopic approach is preferred over traditional surgery, when the surgical approach is required due to lower mortality rates (comorbidities), faster recovery, and lower risk of postoperative adhesions recurrence [32]. Prevention of adhesions/ intestinal obstruction can be achieved by applying various biofilms based on hyaluronic acid, carboxymethyl cellulose, and hyaluronates on the peritoneal surface of the small bowel or of the abdominal cavity, having good results regarding the rates of reinterventions [33,34].

The risk of thrombosis in diabetic patients with colorectal cancer

Thromboembolic phenomena in colorectal cancer can occur in 2.5% of cases, with individual variability depending on body mass index, presence of anemia or sepsis, wound infection, and prolonged mechanical ventilation [35,36]. The risk of deep vein thrombosis occurrence in patients operated via laparoscopic approach versus conventional approach does not differ according to data from a meta-analysis including 9 randomized studies, with a total of 2600 complicated colon cancer patients [37]. The physiopathological mechanisms underlying deep vein thrombosis in patients with colon cancer involve abnormal activation of coagulation and subsequent fibrinolysis [38]. Coagulation Factor Ib is a protein synthesized in the liver that causes platelet adhesion, aggregation, and activation. Elevated levels of this factor can be found in patients with colon cancer secondary to the massive release of proinflammatory proteins, including fibroblast growth factor [39]. In addition, patients with type II diabetes are at increased risk of developing deep vein thrombosis due to endothelial lesions resulting from oxidative stress, advanced glycation end products, and vascular stasis secondary to arteriopathy. All of these are the expression of increased synthesis of TNF-alpha and interleukin 1, which stimulate macrophages and promote thrombin synthesis and factor Xa activation, thus resulting in a hypercoagulable state [40]. Consequently, the association of type II diabetes with colorectal cancer leads to an increased risk of deep vein thrombosis occurrence, the risk being 1.5 times higher in patients with colon cancer and diabetes compared to those without diabetes [38].

Prevention methods for deep vein thrombosis can reduce perioperative mortality [41]. Pharmacological treatment with low molecular weight heparin should be used for at least 30 days, initially in the preoperative period and continued until 30 days postoperatively. Compared to a 10-day anticoagulant treatment regimen, better results have been obtained when it was extended until day 30 of hospitalization [42]. Other methods for preventing deep vein thrombosis in patients with colon cancer and diabetes

can include the use of compression stockings, which have shown good results when combined with pharmacological and mechanical methods [27].

Postoperative infections

Postoperative infections in colorectal surgery are important contributors to mortality and morbidity, being four times more likely to develop than in other gastrointestinal interventions. The main factors leading to their occurrence are represented by advanced age, the degree of wound contamination, or the type of surgery (urgent/elective), as well as previous chemotherapy treatment, prolonged immunosuppression through corticosteroid therapy [43], and diabetes mellitus [44]. Increased blood glucose levels lead to impairment of both the innate immune system (changes in cellular function and of the complement system), as well as the adaptive immune system. In patients with diabetes mellitus, a quantitative decrease in circulating C4d factor and soluble C5b proteins has been observed, the consequence being a significantly decrease in neutralizing gram-negative bacteria [45].

Dendritic cells and macrophages are important effectors of the innate immune system. The function of dendritic cells in diabetic patients is reduced due to a decrease in the maturation of circulating monocytes into functional cells (both on the myeloid and lymphoid lines) and also a decrease in their activation under conditions of hyperglycemia [46,47]. The other affected cell lines are the macrophages. In these patients, a series of pathways are responsible for the alteration of the immune response. By infiltrating them with lipids (secondary to increased amounts of lipoproteins), there is a decrease in their migratory potential and a high rate of apoptosis, and also a decrease in their numbers at the splenic level or in peritoneal fluid [48,49]. The evaluation of their function by exposure to INF-γ and bacterial lipopolysaccharide (LPS) led to a decrease in the expression of adhesion molecules (ICAM), TNF-α, IL-6, and to increased production rate for nitric oxide, thus predisposing patients to develop severe infections [50]. These effects can be eliminated by normalizing blood glucose levels [51]. Another negative consequence on macrophages is the slowing of wound healing, due to their inability of transition from the proinflammatory to the anti-inflammatory phase, which is necessary for tissue repair [52]. The marker of this consequence is revealed by the inhibition of phagocytosis of dead cells, leading to a permanent stimulation of proinflammatory cells through increased synthesis of IL-1β and IL-18 [51].

Neutrophils are involved in the primary defense, having the ability to migrate through the damaged endothelium; the increased level of the C5a component of the complement component has the role of stimulating/ activating them. In diabetic patients, they are capable of synthesizing large amounts of reactive oxygen species, which can lead to damage to various organs [53]. Secondary to oxidative stress generated by hyperglycemia, there is also an increased level of homocysteine, leading to formation of neutrophil extracellular traps (NET) that further affect normal tissues, having the ability to inhibit wound healing [54]. Another effect of hyperglycemia on neutrophils is the inhibition of the TLR4 pathway (due to reduced phosphorylation of NFκB and IκBα receptors), leading to a decrease in their ability to release cytokines and chemokines, as well as to a decrease in their lifespan (due to the presence of increased levels of methylglyoxal), which further leads to increased synthesis of IL6 and IL8 and thus to increased susceptibility to apoptosis [51,55].

High glucose levels lead to the formation of non-enzymatic bonds between different proteins (including immunoglobulins), which results in the alteration of complement system activation and direct phagocytosis [51]. T cells of the adaptive immune system are not spared in patients with diabetes, causing a decreased response to stimulation with phytohemagglutinin (marked by reduced levels of IL-2, 6, TNF-α), even though their numbers are higher compared to individuals with normal glucose levels [56]. As a consequence of all these modifications occurring in hyperglycemia, it can be considered an independent factor for the occurrence of surgical infections, requiring thus an adequate control even if it appears as a result of the acute-phase response [57]. However, in the case of patients with diabetes mellitus, susceptibility to infections remains high even with good glycemic control, necessitating aggressive methods for preventing surgical infections [58].

Mechanical bowel preparation through enemas or laxatives can lead to reduced rates of sepsis or other infectious complications, as well as anastomotic fistulas or ileus [59,60]. The use of prophylactic antibiotics can lead to similar positive results [27]. Simple measures of rigorous hygiene (such as training medical staff, using separate entrances and exits in the operating room) can reduce the risk of infectious complications and hospitalization time for diabetic patients [61]. It is considered that many of the negative infectious consequences that occur in the course of patients with colorectal cancer can be attributed to the negligence of medical personnel, as evidenced by the fact that the implementation of the above measures reduced their rate by up to 40% [62].

Anastomotic fistulas

Anastomotic fistulas represent one of the most frequent complications in colorectal surgery, being associated with high rates of mortality and morbidity [27]. The main factors leading to their occurrence include male gender, smoking, excessive alcohol consumption, NSAIDs and steroids use, as well as a high body mass index, emergency interventions, or marked bacterial contamination [63]. Various biological processes such as inflammation and

immune response, as well as intestinal microbiota or genetic factors appears to be involved in their occurrence [64].

Regarding inflammation at the level of the intestinal wall, it has been observed that there is a close relationship with ischemia at this level, because facultative anaerobic bacteria can consume oxygen, thus creating a hypoxic gradient at this level. As a consequence, mucosal cells express hypoxia-inducible factor (HIF) on the surface, which under normal hypoxic conditions is hydroxylated and helps maintain mucosal barrier function by synthesizing mucins and producing antibacterial peptides. With increasing hypoxic gradient, genes encoding pro-inflammatory factors are activated, being a good stimulator of angiogenesis, inflammation, and immune response, which are primarily mediated by neutrophils that are resistant to ischemia [65,66]. Inhibition of the inflammatory response as the sole target does not seem to decrease the rate of occurrence of anastomotic fistulas, but rather it represents a step in post-resection healing or interaction with the bacterial environment in the lumen [64].

Genetic factors may play an important contribution to risk of developing anastomotic fistulas. Thus, modifications of the prostaglandin endoperoxide synthase 2 and gene polymorphism may lead to more frequent occurrence of rectal cancer than colonic cancer and may affect the function of COX2, an important factor in angiogenesis and post-anastomotic healing [67]. Other observed genetic modifications include those of lipoxygenase-15 (ALOX 15), which has the role of generating anti-inflammatory substances. In the case of the 131G>A mutation, there is an increased risk of rectal cancer occurrence and higher rates of anastomotic fistulas [68]. These modifications explain the higher rates of anastomotic fistulas in operated rectal cancer patients [64].

Microbiota is another factor that can influence the occurrence of anastomotic fistulas. Among the billions of bacterial species in the colon, some have the capacity to degrade collagen or the extracellular matrix. Thus, by eliminating certain strains of E. faecalis with the help of antibiotics, the prevention of fistula occurrence in laboratory animals has been achieved [69]. Some bacterial species have the ability to activate plasminogen, which plays an important role in the occurrence of anastomotic fistulas [70]. In the colon, its presence in large quantities can lead to the activation of matrix metalloproteinase 9 with subsequent collagenolytic effect, thus destroying the proteins of the matrix [71]. The bacteria causing this effect are represented by P. aeruginosa and E. faecalis, colonization with such microbes leading to higher rates of fistula occurrence. A good preventive factor could be the administration of tranexamic acid, which inhibits processes both in vitro and in vivo; thus, the application of enemas with this substance could lead to reduced rates of anastomotic fistulas [70]. Currently, it is not known exactly if there is a direct link between the appearance of fistulas and the presence of certain bacterial strains, but it has been observed that in patients with colon cancer operated on, significant changes occur about 7 days postoperatively in terms of colonization. Such changes appear especially if the patients were exposed to preoperative antibiotic treatment, opioids, or did not receive enteral nutrition, factors that lead to the appearance of germs with a high capacity to degrade collagen [72]. Ultimately, the presence of these factors alone is not sufficient for the occurrence of such complication. In addition to microbiota disorders, there is an increased predisposition to fistulas through chemotaxis secondary to inflammation at the site of the anastomosis and a marked pro-inflammatory response through mucus, peristalsis, IgA, and defensins-mediated mechanisms [73].

Regarding the risk of occurrence of anastomotic fistulas in patients with diabetes mellitus, they are more predisposed due to metabolic disorders, as well as reduced anti-infectious defense mechanisms, causing a delayed healing and thus an increased risk [74]. The risk of developing a fistula in the case of a colorectal intervention associated with diabetes is 1.5 times higher than in a healthy patient, respectively 1.8 times for patients with obesity and perioperative hyperglycemia [75]

The treatment of digestive fistulas is based on localization, size, general conditions of the patient or drained volume There are minimally invasive methods such as endoluminal vacuum-assisted therapy, insertion of polyurethane sponges through endoscopic methods that can thus reduce the dimensions of the abnormal communication, but also the classic methods with resection and formation of a stoma [27]. To reduce their occurrence, various strategies such as strengthening the anastomosis with cyanoacrylate, omental wrapping, or forming mesenteric flaps can be used [76].

Postoperative ileus

Ileus is one of the postoperative complications in colorectal cancer surgery that results in the inability of patients to feed, which can thus lead to the occurrence of anastomotic fistulas or intra-abdominal infections [27]. Factors contributing to its occurrence include advanced age, alcohol consumption, excessive use of opioids, reoperation, or peripheral vascular disease [77]. During surgery, various inflammatory changes occur in the intestinal wall, leading to the recruitment of macrophages, neutrophils and dendritic cells. These can lead to a local inflammatory response that can affect the nerve fibers at this level, leading to dysfunction of normal peristalsis and thus transit disorders [78]. For patients with insulin-dependent diabetes, postoperative ileus is a frequent complication occurring 1.4 times more often than in healthy patients, due to intestinal neuronal impairments secondary to diabetic neuropathy and vascular disorders at this level [79].

Classic treatment for postoperative ileus involves the administration of prokinetics such as metoclopramide, erythromycin, or cisapride, but without spectacular effects in resolving it [80]. Limited use of opioids is recommended, along with widespread use of epidural anesthesia to control postoperative pain. Minimally invasive techniques are encouraged to reduce perioperative pain, leading to early patient mobilization and reduced need for analgesics [81]. Gum chewing is encouraged to prevent ileus, being a simple and inexpensive method that could prevent the occurrence of anastomotic fistulas [82].

Ischemic complications

Intestinal ischemic complications can occur in colorectal surgery, being more common in elderly patients, especially men, and those with associated cardiovascular comorbidities or digestive neoplastic pathology [83]. Diabetes mellitus is also a risk factor for their development, as it favors the occurrence of intestinal microangiopathy, reducing thus the supply of nutrients and oxygen to tissue level, as well as inducing a state of hypercoagulability by increasing the number of platelets [84]. Reduced blood flow leads to increased neutrophil activation with marked release of reactive oxygen species, resulting in cell damage and necrosis depending on the duration of hypoperfusion and the affected vascular territory [85]. Treatment of vascular ischemia involves fluid administration and electrolyte re-balancing to promote increased cardiac output and intestinal perfusion, discontinuation of vasoactive treatment [86], interruption of enteral feeding (to reduce intestinal energy consumption), and administration of broad-spectrum antibiotics [86]. Curative-dose anticoagulant treatment is not indicated in the case of acute intestinal disorders, but prophylactic treatment is recommended [87]. Surgical treatment is indicated in cases where there are clear signs of endoscopic/imaging gangrene or symptomatic surgical acute abdomen, involving resections or (if possible) vascular reperfusion [85].

Conclusions

In conclusion, postoperative complications in colorectal surgery (such as anastomotic fistulas, postoperative ileus, and intestinal ischemia) require a careful monitoring, based on a comprehensive understanding of the contributing factors. Patients with diabetes mellitus, especially those requiring insulin, exhibit an increased susceptibility to such complications, due to the complex interplay of metabolic disturbances, impaired immune response, as well as vascular and neural impairments. In addressing these postoperative challenges, a multidisciplinary approach involving surgeons, anesthesiologists, and other healthcare professionals is essential. Advances in understanding the complex relationships between genetic predisposition, immune response, and microbial influences offer the prospect for more targeted preventive measures as well as improved outcomes for patients undergoing colorectal surgery.

Compliance with ethical standards

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript. Informed consent was obtained from all subjects involved in the study.

Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

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