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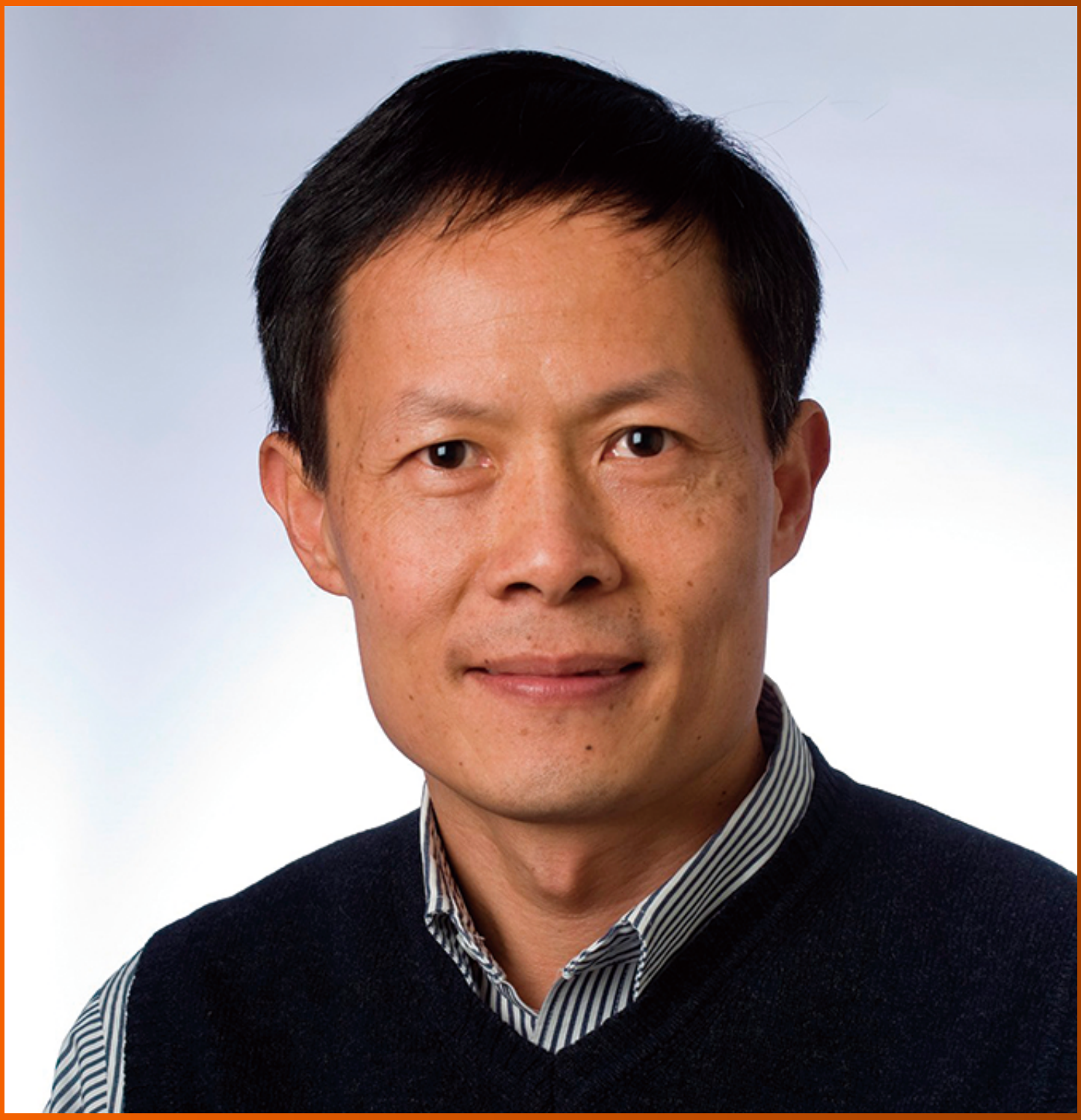

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ABOUT COVER

Peer Reviewer of *World Journal of Experimental Medicine*, Cory J Xian, PhD, Research Professor, UniSA Clinical and Health Sciences, University of South Australia, Adelaide, SA 5001, Australia. cory.xian@unisa.edu.au

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MINIREVIEWS

Bariatric surgery outcomes following organ transplantation: A review study

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Abstract

Weight gain is a frequent postoperative complication following a solid organ transplant which can be solved by bariatric surgery. The outcomes of bariatric surgery among patients with an organ transplant history are always a challengeable subject for surgeons and surgery candidates. In this review article, we aim to investigate the existence literature about the rates of morbidity and mortality, frequent complications in terms of graft function, remission in diabetes, hypertension, pulmonary and cardiovascular disorders, hepatic and renal functions, and immunosuppressive stability, as well as the safety of bariatric surgery among patients.

Key Words: Bariatric surgery; Organ transplantation; Complications

Core Tip: In this minireview article, we try to provide a broad introduction to the impacts of bariatric surgery on organ transplantation outcomes rather than as an exhaustive review. Moreover, this review will focus on major transplantations and type of bariatric surgery among morbidly obese patients. Within the broad categories of organ transplantation, we then conclude with remarks about the outcomes of bariatric surgery among patients with combined organ transplantation. Where possible, the readers are suggested to refer to the numerous comprehensive clinical studies reporting the predictors of adverse outcomes of organ transplantation following bariatric surgery.

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INTRODUCTION

Obesity is a frequent complication among patients who underwent solid organ transplantation, and may consequently affect the transplant population at multiple levels[1,2]. Graft function depends not only on the management of immune processes but also on the optimal control of chronic diseases, especially obesity and metabolic syndrome, which may lead to a number of disorders exerting adverse effects, including to the transplanted organ[3]. Obesity in transplantation patients may also negatively impact preoperative and long-term outcomes after bariatric surgery[4,5]. Based on previous reports, obesity was linked to a higher odds of biopsy-proven acute rejection, mortality, allograft loss, and the development of diabetes[6]. Therefore, this study aims to compare the clinical outcomes of bariatric surgery among patients with prior organ transplantation. In this mini-review article, we tried to provide a broad introduction to the impacts of bariatric surgery on organ transplantation outcomes rather than as an exhaustive review. Moreover, this review will focus on major transplantations and type of bariatric surgery among morbidly obese patients including kidney transplantation, liver transplantation, heart transplantation, and sleeve gastrectomy (SG); pancreas transplantation and gastric banding surgery; lung transplantation and robotic Roux-en-Y gastric bypass (RYGB). Within the broad categories of organ transplantation, we then conclude with remarks about the outcomes of bariatric surgery among patients with combined organ transplantation. Where possible, the readers are suggested to refer to the numerous comprehensive clinical studies reporting the predictors of adverse outcomes of organ transplantation following bariatric surgery.

KIDNEY TRANSPLANTATION AND BARIATRIC SURGERY

The problem of obesity in renal transplant recipients has been well documented. Based on previously published reports, kidney recipients with obesity demonstrated enhanced rate of comorbidities such as respiratory and cardiovascular diseases, diabetes mellitus or posttransplant diabetes mellitus, dyslipidemia, and even wound complications[7-9]. Elli *et al*[10] evaluated the outcomes of SG in six patients who had a kidney transplant. There were no significant differences in excess weight loss (EWL) or percent of weight loss (WL) between the renal recipient group and patients without a history of kidney transplant. In addition, no preoperative and serious postoperative complications were observed in the transplant group. In another study, four kidney transplant patients diagnosed with hypertension (all subjects) and type 2 diabetes (T2D) underwent SG and 45% of EWL was observed 12 to 24 mo after surgery[1]. The authors reported a significant reduction in antihypertensive medications and complete remission of T2D one year after SG[1]. Significant weight loss, improvement of obesity-related conditions, preservation of graft function, and the estimated glomerular filtration rate (eGFR) were enhanced significantly in the subjects[1]. Furthermore, five renal recipient patients underwent bariatric surgery[4] RYGB and one SG and experienced 50% of EWL at 2 years after procedure. Preoperative evaluation revealed five subjects with hypertension, two with T2D, and one with chronic heart failure among the patients. After surgery, no postoperative complications and no alteration to the dosage of the immunosuppressant drugs were recorded[11]. However, in another study among ten patients with a history of kidney transplants, just two cases needed higher doses of tacrolimus and one decreased based on serum level[7]. Gheith *et al*[12] in 2017 reported a study to shed light on the effects of bariatric surgery on the outcomes of renal transplant recipients among 22 bariatric patients with a history of kidney transplant and 44 nonbariatric control subjects with a kidney transplant history. The overweight nonbariatric control group received a more potent induction immunosuppression compared to bariatric patients. In addition, no differences in graft functions or new onset of T2D were recorded in 22 bariatric patients with a history of kidney transplant compared to the control group. In a well-designed study, the outcomes of bariatric surgery were evaluated among 26 patients with a history of kidney transplant. However, the patients experienced more than 50% of EWL improvement in comorbidities without serious graft rejection, and declined tacrolimus blood levels (but remained within the therapeutic range), but the surgical risk was higher than the regular bariatric surgery population[13]. Table 1 demonstrates more studies on the outcomes of bariatric surgery in patients with a history of organ transplantation. In the most recent study, among 38 patients with solid organ transplantation, eight had a kidney transplant. Comorbidity-related medications such as tacrolimus were declined in most patients, while two subjects experienced transplant organ rejection after bariatric surgery[14].

Table 1 Outcomes of bariatric surgery in patients with a history of organ transplants

Organ	Type of bariatric surgery	Patients (*n*)	Potential risks	Mean BMI or weight changes after BS	Comorbidities/improvements	Ref.
Liver	RYGB	7	Gastric staple line leakage, EWL	From 44.34 ± 6.08 kg/m^2 to 26.47 ± 5.53 kg/m^2	DM, HTN, GERD, vascular disease, and OSA	Al-Nowaylati *et al*[17]
	LSG	12	Infections and leaks	Mean BMI decrease 12.9 kg/m^2	Nine out of 12 patients had DM and metabolic syndrome; four out of 12 patients showed a complete improvement after LSG	Tsamalaidze *et al*[27]
	Open SG	1	-	From 47 kg/m^2 to 29.8 kg/m^2	DM and arterial HTN	Butte *et al*[28]
	RYGB, LSG, jejunoileal bypass SG	11	Organ insufficiency	Mean BMI 28.3 ± 5.8 kg/m^2	Early surgical site infection, and bleeding	Safwan *et al* [29]
Kidney	Gastric bypass	5	-	Mean WL of 33 kg	DM, HTN, and hyperlipidemia	Arias *et al*[11]
	RYGB, LSG	5	-	50% EWL at 2 yr	DM, HTN, hyperlipidemia, polycystic ovarian syndrome, peripheral vascular disease, and CHF	Szomstein *et al*[7]
	LSG	10	Acute renal failure and sleeve stricture	57% EWL at 6 mo, and 75% EWL at 12 mo	Not mentioned	Golomb *et al* [30]
		6	-	44.1% EWL at 3 mo, and 75.9% EWL at 12 mo	Morbid obesity	Gazzetta *et al* [31]
Liver and kidney	LSG	9	Mesh dehiscence after a synchronous incisional hernia repair, bile leakage, and dysphagia that required reoperation	61% EWL	Mesh dehiscence after synchronous incisional hernia repair, bile leak, post-operative dysphagia	Lin *et al*[18]
Heart	RYGB and LSG	2	-	From 37.5 kg/m^2 to 27.5 kg/m^2 at 12 mo	HTN, hiperlipidemia, anemia, and hipomagnesemia	Tsamalaidze *et al*[32]
Heart and kidney	Vertical banded gastroplasty	2	Inadvertent laceration of the pancreas resulting in pseudocyst which may need percutaneous and then surgical drainage	Mean WL of 54 and 56 kg	Not mentioned	Rex *et al*[33]

BMI: Body mass index; BS: Bariatric surgery; RYGB: Roux-en-Y gastric bypass; EWL: Excess weight loss; LSG: Laparoscopic sleeve gastrectomy; SG: Sleeve gastrectomy; WL: Weight loss; DM: Diabetes mellitus; HTN: Hypertension; GERD: Gastroesophageal reflux disease; OSA: Obstructive sleep apnea; CHF: Congestive heart failure.

LIVER TRANSPLANTATION AND GASTRIC BYPASS

There is a positive correlation between body mass index (BMI) and nonalcoholic fatty liver disease (NAFLD), and individuals with obesity undergoing liver transplantation may be at enhanced risk for NAFLD recurrence[15,16]. Whereas some experts prefer to do the liver transplantation first, some others have suggested gastric bypass before liver transplant. In a study on seven patients with a history of orthotopic liver transplantation who underwent RYGB, two deaths in subjects with hepatitis C were reported 6 and 9 mo following bariatric surgery[17]. Gastric bypass may have contributed to the death of one case owing to multiple organ dysfunction syndrome. The other patients experienced improved gylcemic control, therapeutic weight loss, and balanced high-density lipoprotein levels with continued dyslipidemia in a long-time follow-up[17]. In another report, among five liver-recipient patients undergoing SG, five and four in preoperative assessment were diagnosed with hypertension and T2D, respectively. In postoperative screening, the patients illustrated a significant reduction in antihypertensive medications including mycophenolate 720 mg and tacrolimus 2 mg, and completed remission of T2D, and graft function remained preserved in subjects one year after SG[1]. Lin *et al*[18] reported the outcomes of SG in nine patients with prior liver transplant. In the first month after SG, three subjects

were diagnosed with postoperative complications including dysphagia that required reoperation, bile leak from the liver surface requiring laparoscopic drainage, and mesh dehiscence after synchronous incisional hernia repair. Hepatic and renal functions remained stable and no graft rejection was reported after surgery. In a case report study on a 51-year-old male liver recipient, he was diagnosed with steatohepatitis of the graft, gained 30 kg after organ transplant, and was on an oral hypoglycemic agent with HbA1c of 8%. After laparoscopic SG, completed remission in diabetes, reduction in BMI from 42 to 34, and stable graft functions were reported[19]. In one of the most recent studies on 19 cases with prior liver transplant undergoing SG or robotic RYGB, one patient was readmitted for abdominal pain owing to gastric ulcer[14] and related comorbidities were decreased in most of patients[10,14]. There were no organ rejections in this study at the 12-mo follow-up[14]. The tacrolimus blood levels declined to 4-6 ng/mL 6 mo after operation[13].

HEART TRANSPLANTATION AND SLEEVE GASTRECTOMY

In a previously mentioned study by Khoraki *et al*[1], one patient with a history of heart transplant was diagnosed with hypertension. The preferred surgery was SG and after the procedure, the subject experienced 45% of EWL and reduction in antihypertensive medications. Moreover, the left ventricular ejection fraction enhanced by 10% in the patient was reported after surgery. Significant weight loss, improvement of obesity-related conditions, and preservation of graft function were observed after SG [1]. In another study on six cases with heart transplant, three subjects underwent SG and three patients underwent robotic RYGB. One patient died 20 mo after robotic RYGB owing to the adverse effects of the tricuspid valve replacement, not directly related to bariatric surgery. One subject required early readmission due to abdominal pain and shortness of breath. No leaks were documented in either group [14]. The comorbidity-related medications were decreased in other cases[1,19].

PANCREAS TRANSPLANTATION AND GASTRIC BANDING SURGERY

Regarding pancreas recipients, there are no technical modifications to be considered. RYGB is not performed in these patients because of bowel drainage[10]. In a report, two patients with pancreas transplant maintained normal glycemic serum levels with HbA1c levels of 5.8% and 5.3%, respectively, at the one-year follow-up[20]. Weight gain in these patients may induce insulin resistance and return to insulin therapy despite proper graft function. Furthermore, calcineurin inhibitors for maintenance immune suppression can cause insulin resistance, and they are also responsible for weight gain post-transplantation[10]. However, laparoscopic gastric banding surgery to treat insulin resistance in a pancreas transplant recipient yielded good short-term outcomes[20].

LUNG TRANSPLANTATION AND ROBOTIC RYGB

For patients with lung transplant, robotic RYGB seems a preferable method compared to other types of weight loss surgery due the high reported rate of postoperative reflux[21,22]. In a study on two patients with lung transplant, no organ rejection was reported and comorbidity conditions declined significantly after surgery[14].

OUTCOMES OF BARIATRIC SURGERY AMONG PATIENTS WITH COMBINED ORGAN TRANSPLANTATION

The outcomes of bariatric surgery in patients with combined transplantation are one of the principal studies that have been performed by some researchers, but more studies with a long-term follow-up period are required to conclude the efficiency of weight loss surgery in this population. For instance, combined kidney-pancreas transplantation is a treatment option for end-stage diabetic nephropathy. Post-transplant weight gain enhances the risk for posttransplant comorbidities and death caused by pulmonary and cardiovascular disorders. Gastric banding is an established treatment for moderate morbid obesity for this population[20]. Based on reports on kidney pancreas recipients, although no organ rejection, declined HbA1c levels and significant weight loss were reported[14,20,23], but no reduction in medication doses was reported postoperatively[23]. In another study on a 65-year-old patient with combined kidney-liver transplant, 30 kg weight gain with the risk of graft impairment was reported 4 years after transplant. It has been reported that, after weight loss surgery, although the surgical risk was higher than the regular bariatric patients[13], BMI declined significantly with stable graft functions[19] and no development of diabetes[14,19] in patients with a history of kidney-liver

Table 2 Dose adjustment of immunosuppressive drugs following bariatric surgery in patients with a history of organ transplants

Organ	Type of bariatric surgery	Patients (*n*)	Immunosuppressant adjustment compared to patients without organ transplants	Ref.
Liver	LSG	12	No changes	Tsamalaidze *et al*[27]
		9		Lin *et al*[18]
	Bariatric surgery	56		Lazzati *et al*[34]
Kidney	Gastric bypass	2	Increased doses of sirolimus, tacrolimus, and mycophenolate mofetil	Rogers *et al*[35]
	Laparoscopic gastric bypass	5	No changes	Arias *et al*[11]
	LSG	10	Two patients with increased doses of tacrolimus and one decreased	Golomb *et al*[30]
		6	No changes	Gazzetta *et al*[31]
		5	Decreased dose of cyclosporine	Szomstein *et al*[7]
	Biliopancreatic diversion	1	No changes	López Deogracias *et al*[36]
Heart	Laparoscopic gastric banding, laparoscopic robotic-assisted RYGB, and LSG	3	No changes	Tsamalaidze *et al*[32], Ablassmaier *et al*[37]
Heart and kidney	Vertical banded gastroplasty	1	Changes based on serum level	Rex *et al*[33]

LSG: Laparoscopic sleeve gastrectomy; RYGB: Roux-en-Y gastric bypass.

transplantation. Immunosuppressive stability was enhanced from 39% to 47% after bariatric surgery in this population[13]. Table 2 presents more details of studies related to the immunosuppressant changes following bariatric surgery in patients with a history of organ transplants.

PREDICTORS OF ADVERSE OUTCOMES OF ORGAN TRANSPLANTATION FOLLOWING BARIATRIC SURGERY

Ethnicity and its impact on the outcomes of bariatric surgery among patients with a transplant history, are a remarkable issue that has been addressed by Edwards *et al*[24] in a recent report. In this survey on 335 patients from white and black races, preoperatively, black subjects were more likely to have hypertension and dialysis dependent chronic disease and be on chronic steroids. Nonetheless, mortality and morbidity rates were similar in both groups. Postoperatively, the black population were prone to have higher rates of renal failure, pulmonary disorders, and emergency readmissions, higher overall bariatric-related morbidity, and higher rates of pneumonia and progressive renal insufficiency compared to the white group. Nevertheless, race was not found to be an independent predictor of adverse outcomes following SG or RYGB in subjects with prior solid organ transplantation[24]. The same results can be seen in another cohort study with 610 patients with organ transplant and 320000 cases without organ transplant. While previous transplant subjects experienced a higher incidence of readmissions, surgical complications, and medical issues than the other group, but no difference in the incidence of death was observed[25]. On the other side, among patients with prior organ transplant, longer operative time and increased rates of morbidity, surgical site infection, acute and progressive renal failure, myocardial infarction, bleeding, and venous thromboembolism are undeniable after bariatric surgery[26]. Considering the potential for poorer outcomes in overweight people with prior solid organ transplant, there is significant interest in identifying optimal modalities to achieve significant and durable weight loss, including metabolic and bariatric surgery.

CONCLUSION

Cumulatively, reports suggested that bariatric surgery, regardless of the type of procedure (sleeve *vs* gastric bypass) and surgical approach (robotic assisted *vs* conventional laparoscopic), ensures significant weight loss and improvement of related conditions, together with good immunosuppressive maintenance, along with the absence of serious graft rejection or dysfunction and with a trivial mortality rate in this high surgical risk population. Due to the lack of a large size survey, we are unable to expand our analyses by bariatric procedure type and surgical approach. These are potential confounders that

may have influenced results. Further studies to assess bariatric surgery outcomes by organ transplant subtype and risks of organ rejection are necessary to advance our knowledge on this issue. Obesity medicine experts may choose to use this review article to educate patients with organ transplant about bariatric surgery and the options for them to promote weight loss postoperatively.

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FOOTNOTES

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LETTER TO THE EDITOR

Performance of a serological IgM and IgG qualitative test for COVID-19 diagnosis: An experimental study in Brazil

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Abstract

Qualitative antibody tests are an easy, point-of-care diagnostic method that is useful in diagnosing coronavirus disease 2019, especially in situations where reverse transcription-polymerase chain reaction is negative. However, some factors are able to affect its sensitivity and accuracy, which may contribute to these tests not being used as a first-line diagnostic tool.

Key Words: Serological test; IgM; IgG; COVID-19; Diagnosis; Antibody

Core Tip: In this study we compared a quantitative enzyme-linked immunosorbent assay test that detects antibodies against the severe acute respiratory syndrome coronavirus 2 S1 epitope with the qualitative test. Our results demonstrate that the quantitative tests have significantly higher sensitivity rates, evidencing limitations in the use of the qualitative antibody detection test as a first-line diagnostic tool.

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TO THE EDITOR

We read with interest a retrospective study that assessed whether serological rapid antibody tests would be effective in the diagnosis of coronavirus disease 2019 (COVID-19) pneumonia in patients whose reverse transcription-polymerase chain reaction (RT-PCR) tests were negative, despite having radiological and clinical features consistent with this condition[1]. The authors evaluated and reported the clinical aspects, laboratory results, and radiological findings of 80 suspected COVID-19 patients who had at least two negative consecutive RT-PCR tests and underwent rapid serological antibody testing. In this sense, Colloidal Gold severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) IgG/IgM Rapid Test (Beijing Hotgen Biotech Co., Ltd) was used, which is a lateral flow chromatographic immunoassay detecting total antibodies produced against the SARS-CoV-2. Therefore, the specific serological total IgM/IgG antibodies against SARS-CoV-2 were detected in 22 of these patients. The authors, then, concluded that rapid serological antibody tests may be a suitable alternative in the diagnosis of suspected COVID-19 cases, especially in highly suspected cases with negative RT-PCR results.

Regarding COVID-19 diagnosis, nucleic acid amplification tests are considered as the most sensitive ones, with RT-PCR being the gold standard method, with an overall sensitivity of 0.96 (95% confidence interval [CI]: 0.93-0.98) and false negative rate of 0.06 (95%CI: 0.04-0.08), according to a recent meta-analysis[2]. On the other hand, chest CT scan is another fundamental piece for the diagnosis of COVID-19 and monitoring of the evolution of the patient's condition[3]. Although the identification of typical lesions caused by SARS-CoV-2 is relevant, presenting a high sensitivity, it has a low specificity, since imaging findings may also be present in other viral infections with similar ongoing symptoms to COVID-19[4].

In this sense, serological tests emerged in the SARS-CoV-2 pandemic to diagnose the infection after 14 d, since this is the cut-off period for reliable detection of amplification methods[5]. One study analyzed samples of SARS-CoV-2-positive patients by RT-PCR test, SARS-CoV-2 RT-PCR-negative patients with a clinical picture of COVID-19, and controls. General sensitivity for IgG was around 80.0% for the chemiluminescence enzyme immunoassays (CLIA), enzyme-linked immunosorbent assays (ELISA), and lateral flow immunoassays (LFIA) and the sensitivity of IgG reached 100.0% when the blood was obtained 15 d after the symptoms appeared. Overall, IgG specificity was ≥ 95.8%. In addition, the same study identified an IgM sensitivity of 81.8% and specificity of 95.3% in LFIA, which were 100% after 15 d of symptom onset[6]. Otherwise, in a meta-analysis study, the authors verified the pooled sensitivity and specificity of IgG and IgM of the above cited tests and observed wide 95%CIs, varying from 46.2% to 100% (CLIA), 75.6% to 90.9% (ELISA), and 49.3% to 79.3% (LFIA), which led the authors to emphasize that the data do not support the continued use of existing point-of-care serological tests and that further studies are needed to assess the accuracy of serological tests[7].

Another meta-analysis study by analyzing RT-PCR, immunological tests, and computed tomography (CT) demonstrated that the combination of IgM and IgG antibodies yielded a sensitivity of 84.5% and specificity of 91.6%, the RT-PCR test in sputum samples and CT obtained a sensitivity of 97.2% and 91.9%, respectively, but CT had a low specificity (25.1%). The authors corroborated the consensus of the RT-PCR method being the gold standard, but recommended the combination of different tests to improve the sensitivity and specificity of the diagnosis[8].

In respect to our study, the experience with EDI™ Novel Coronavirus COVID-19 ELISA Kit Flyer IgM and IgG (Epitope diagnosis Inc São Diego, EUA) qualitative test differs from the conclusion of Yıldırım *et al*[1]. Our team compared a quantitative ELISA test that detects antibodies against the SARS-CoV-2 S1 epitope with the EDI™ Novel Coronavirus COVID-19 ELISA Kit Flyer IgM and IgG (Epitope Diagnosis Inc San Diego, USA), which is a qualitative test, that is, it indicates the presence or absence of the virus without quantifying the viral load[9]. Eighty Brazilian patients were included in this study (47 adults, mean age of 41.5 ± 12.2, and 33 children, mean age of 9.7 ± 2.9), and among them, 21 were RT-

PCR positive for COVID-19 and 59 were negative.

Overall, our results demonstrated that the sensitivity, specificity, accuracy, positive predictive values and negative predictive values of IgM detection were 19.05%, 100.0%, 78.7%, 100.0% and 77.6%, respectively, whereas the corresponding values of IgG were 38.1%, 100.0%, 83.7%, 100.0% and 81.9%, respectively. Notably, four children included in our study had severe multisystem inflammatory syndrome (MIS-C), which in most cases is a post-acute manifestation of COVID-19. Among the four children with MIS-C, two were RT-PCR negative, IgM was not detected in the serum of these children, but IgG was positive in three of them. Therefore, more accurate tests are necessary, not only to improve the diagnosis of COVID-19, but also of MIS-C especially because the direct detection of SARS-CoV-2 is less frequent in this severe disease. It is worth mentioning that, as shown in other studies, when comparing a quantitative ELISA test with a qualitative test, the sensitivity was much higher in the first one, even without differences in the duration of time from the onset of the first symptoms and blood collection (data not shown).

To conclude, despite the putative benefit of qualitative antibody tests in diagnosing COVID-19 in patients in whom RT-PCR test was negative, the low sensibility of some testing kits limits their use as a first-line diagnostic tool. Thus, we suggest qualitative tests to be used as an adjunctive tool in specific situations, of note: (1) In patients whose clinical picture indicates COVID-19, yet RT-PCR is negative; and (2) In the identification of past infections, until advances in the field improve the performance of rapid tests or further studies clarify the divergent results regarding the sensibility and specificity of these diagnostic methods.

FOOTNOTES

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LETTER TO THE EDITOR

Diet and nutrition against inflammatory bowel disease: Trick or treat(ment)?

Salvatore Greco, Beatrice Bonsi, Nicolò Fabbri

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Abstract

Even if the relationships between nutrition and inflammatory bowel disease (IBD) remain underexplored, the current literature is providing, day by day, much more evidence on the effects of various diets in both prevention and treatment of such illnesses. Wrong dietary habits, together with other environmental factors such as pollution, breastfeeding, smoke, and/or antibiotics, are among the theoretical pathogenetic causes of IBD, whose multifactorial aetiology has been already confirmed. While some of these risk factors are potentially reversible, some others cannot be avoided, and efficient treatments become necessary to prevent IBD spread or recurrence. Furthermore, the drugs currently available for treatment of such disease provide low-to-no effect against the symptoms, making the illnesses still strongly disabling. Whether nutrition and specific diets will prove to effectively interrupt the course of IBD has still to be clarified and, in this sense, further research concerning the applications of such dietary interventions is still needed.

Key Words: Crohn's disease; Ulcerative colitis; Inflammatory bowel disease; Diet; Nutrition; Treatment

Core Tip: The incidence of inflammatory bowel disease (IBD) is alarmingly growing worldwide, and there is still no efficient drug able to induce complete remission since IBD spreads. There is currently no consensus in the medical community about nutritional treatment for the IBD patients, and the role of diet in the disease course is often underestimated. Diet and nutrition seem to have a role not only in preventing the onset of the disease, but also in inducing and keeping temporary remission. Whether specific diets have potential to cure the disease is still uncertain and much research is still needed to clarify their role in this sense. In our opinion, diet and nutrition should be classified as pure treatments against IBD, as it happens for steroids, azathiopirine, mesalazine, or others, and their administration should be indicated by nutrition specialists, with the greatest degree of customization of dosages and dietary plans.

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TO THE EDITOR

Inflammatory bowel disease (IBD) is generally multifactorial and usually characterised by exacerbated immune response and epithelial barrier dysfunction. The intestinal epithelium is appointed to defend the host from bacterial and other micro-organisms' invasion and to control the passage of water and electrolytes. In the case of IBD, the integrity of the epithelial barrier gets severely compromised, with consequent destabilization of intercellular junctions (tight and adherens junctions)[1,2].

Pharmacological treatments include anti-inflammatory drugs, such as steroids, mesalazine, biological anti-tumor necrosis factor-α, or immunomodulators such as azathiopirine[3], but they are usually not sufficient to keep disease remission or show low-to-no effects against temporary symptoms. Moreover, the high incidence of side effects has to be considered. Substantially, there is still no efficient drug able to induce complete remission since IBD spreads. In this sense, the development of alternative and "safer" treatments for preventing the disease or controlling its course, has taken hold over the last decade. Diet itself, together with smoke, pollution, breastfeeding, and/or antibiotics, is among the most important environmental factors predisposing to IBD. The beneficial effect of diet on both development and duration of the remitting phases is already known, even if nutritional supplements and macro- and micro-nutrients should be always adapted to patients, as they have different roles in preventing or inducing remission in Crohn's disease (CD) or ulcerative colitis (UC)[4]. Furthermore, we would like to stress another aspect of the pathogenesis of such diseases, which is represented by intestinal dysbiosis (the altered composition of the gut microbiota), historically linked to numerous gastrointestinal diseases (including malignancies and chronic hepatitis B and often precipitated by the constant and increasing use of antibiotics in our society[5]. The current literature is full of examples of how intestinal dysbiosis can potentially affect the epithelial integrity, progressively leading to the development of chronic inflammatory diseases, but the exact mechanism of such damage is still far from being fully understood and deserves some more attention.

The gut microbiota of individuals with IBD is characterized by low microbial diversity in general, and a higher concentration of pathobionts such as adherent/invasive *Escherichia coli* and *Clostridium difficile*, Proteobacteria, and Actinobacteria, even if patients with CD have greater microbiota dysbiosis than those with UC[6-9].

Compared to the Mediterranean diet, the Western-style diet (WSD) contains significantly higher amounts of simple refined carbohydrates, saturated fat, red meat, dairy, and industrialized foods. Although the relationship between the WSD and IBD has only been partially studied, the WSD involves the use of nutrients capable of eliciting a direct or indirect pro-inflammatory effect on the intestine through alterations in the equilibrium among the immune system, microbiota, and intestinal barrier[10, 11].

Food-induced changes in the microbiota have not yet been fully studied, but it is known that higher intakes of fibers, while favouring the production of small chain fatty acids by the microbiota, can exacerbate the symptoms in patients with IBD, especially during the acute phases. Furthermore, the excess of refined carbohydrates and dairy products and proteins has been shown to alter the gut microbiota by reducing the abundance of bacteria such as Roseburia and *Eubacterium rectale*, where are considered beneficial to health due to their ability to produce butyrate[12-14]. However, the most compelling studies on IBD have focused on the risk of high-saturation polyunsaturated fatty acids as a consequence of high meat consumption (especially red meat).

Another possible causative factor is represented by gluten: Its digestion gives rise to toxic and antigenic peptides (especially alpha-gliadin peptides), which can interfere not only with the tight junctions between enterocytes but also with enterocyte survival by affecting the whole intestinal barrier.

High-fat diets, in general, can lead to higher storage of secondary bile acids, such as deoxycholic acid, which can inhibit the growth of specific bacterial phyla such as Bacteroidetes and Firmicutes, thus resulting in intestinal dysbiosis similar to that found in IBD[15]. Also, the negative effect of non-caloric artificial sweeteners on the composition and functioning of the microbiome has been clearly highlighted by several studies, resulting in an increased risk of obesity, insulin resistance, and inflammation[16,17].

Enteral nutrition (EN), either elemental or nonelemental, is considered a plausible alternative to drugs for inducing IBD remission, and it is able to fight the nutritional gap induced by intestinal malabsorption during the acute phase of the disease. EN has been shown to have an anti-inflammatory effect in children with CD, and it seems to have a significant impact in the cascade of pathogenesis, even if the underlying mechanisms of action are not fully understood[18-20]. Basically, although conducted on small sized samples of patients, most studies seem to suggest that IBD-dedicated diets should reduce the overall quantity of meat, eliminate red and processed meat, and eliminate or strongly reduce gluten and dairy products (*i.e.*, caseins), with the only exceptions of yogurt and kefir.

According to Levine *et al*[20] and after a quick review of the literature dedicated to this topic and with current knowledge, we can state that it is fundamental to customize the choice of micro- and macro-nutrients and supplemental nutrition for each patient; at the same time, it would be excessively superficial to consider the administration of such aids as tricks, only able to delay the spread of the IBD or the recurrence of their acute phases. In our opinion, diet and nutrition have to be classified as pure treatments against IBD, as it happens for steroids, azathiopirine, mesalazine, or others, and their administration should be indicated by nutrition specialists, with the greatest degree of customization of dosages and dietary plans.

FOOTNOTES

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