Current Nutrition Reports (2023) 12:229–237
https://doi.org/10.1007/s13668-023-00464-1

REVIEW

Synbiotics and Surgery: Can Prebiotics and Probiotics Affect Inflammatory Surgical Outcomes?

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Accepted: 7 February 2023 / Published online: 30 March 2023

Abstract

Purpose of Review Prebiotics, probiotics, and synbiotics have received increasing attention over the years for their beneficial impact on the gut microbiome and for their systemic anti-inflammatory effects. They have also been shown to improve surgical outcomes. Here, we review the inflammatory effects of surgery as well as the data which suggests a benefit of prebiotics, probiotics, and synbiotics taken in the perioperative period.

Recent Findings Synbiotics and fermented foods may have an even greater anti-inflammatory effect than probiotics or prebiotics alone. Recent data suggest that the anti-inflammatory effects and microbiome changes brought on by prebiotics, probiotics, and synbiotics have the potential to improve surgical outcomes. We highlight the potential to alter systemic inflammation, surgical and hospital-acquired infections, colorectal cancer formation, recurrence, and anastomotic leak. Synbiotics could also impact metabolic syndrome.

Summary Prebiotics, probiotics, and especially synbiotics may be extremely beneficial when taken in the perioperative period. Even short-term gut microbiome pre-habilitation could alter surgical outcomes significantly.

Keywords Synbiotics · Fermented foods · Surgical outcomes · Surgical site infections · Inflammation

Introduction

For many years, there has been increasing interest in the study of the gut microbiome. In 1992, probiotics were defined as "a preparation of or a product containing viable, defined microorganisms in sufficient numbers, which alter the microflora (by implantation or colonization) in a compartment of the host and by that exert beneficial health effects in this host" [1]. In more recent years, interest has turned to prebiotics, or "non-digestible food ingredients (fiber) that beneficially affect the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon" [1]. These bacteria transform the fiber into short chain fatty acids which exert beneficial local and systemic effects [2]. The gut microbiome is dynamic and can be transformed quickly by supplements containing bacteria (probiotics) or fiber (prebiotics). In fact, a change in the amount of fiber in a diet can alter the composition of the microbiome in as little as 24 h [3]. Synbiotics, often in the form of fermented foods, combine prebiotics and probiotics, which act synergistically. In a 2012 study comparing a synbiotic supplement to a prebiotic, the synbiotics decreased circulating levels of interleukin (IL)-16 by approximately 50%, compared with the single prebiotic alone [4]. Among other effects, prebiotics, probiotics, and synbiotics act as anti-inflammatory supplements with the latter perhaps being the most effective. Because surgery has a clear inflammatory effect on the body [5], in this review, we explore the ways in which prebiotics, probiotics, and synbiotics may play a role in modulating the immune response in the perioperative period, and the extent to which they may affect surgical outcomes.

Inflammation

Inflammation, although required for the normal response to invading organisms and stress, when excessive and uncontrolled can precipitate a variety of chronic diseases

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and subdues healing in many forms. Inflammatory syndromes which fail to resolve can lead to dysfunction in a wide range of organ systems including vascular disease, metabolic syndrome, multiple gastrointestinal conditions, and neurologic diseases. In addition, unresolved inflammation can even lead to neoplastic disease, which is well understood in the case of chronic liver disease and hepatocellular carcinoma. Appropriate inflammatory signaling is vital to immune system function and excessive inflammation is detrimental to healing from surgical and medical diseases.

Tissue injury from surgery initially promotes an inflammatory state. The body's immediate response to surgery is the upregulation of the innate immune system, eliciting a furor of neutrophils, monocytes, and cytokines including IL-1β, IL-6, and tumor necrosis factor α (TNF-α). The goal of upregulation of the innate immune system is to target infection, limit tissue damage, and eliminate destroyed cells in order to promote healing [6, 7]. This initial inflammatory state triggers suppression of the adaptive immune system by dampening T cell proliferation in order to quell a hyper-inflammatory response which may hinder appropriate healing [5, 8]. The anti-inflammatory phase is prolonged in comparison to the initial heightened innate immune response and is associated with increased levels of anti-inflammatory cytokines including IL-1, IL-4, and IL-10, and bioactive lipids [6, 9].

Immune system stability is important for healing from surgery and disease, and a swing too far in either direction can lead to immune dysfunction and suppression. On one hand, hyper-inflammation defined by elevated inflammatory markers can lead to suppressed immunity. This is evidenced by recent data from the COVID-19 pandemic suggesting that elevated inflammatory markers correspond with more severe disease and worse outcomes [10]. Suppression of the adaptive immune system as seen in the delayed anti-inflammatory response to surgery can put the postoperative patient in an immunosuppressed state as well, and at risk for sepsis and even multi-system organ failure [5].

The immune system is a complex web of pathways modulated by ON/OFF signaling molecules. A paucity or overabundance of any one of these molecules may cause extreme effects downstream. In the context of post-surgical healing, there is scarcity of data directly linking levels of specific inflammatory molecules with specific surgical outcomes, but the need to avoid abundant inflammation is clear. For example, elevated inflammatory cytokines have been linked to postoperative delirium, excessive muscle catabolism, and prolonged hospital and ICU stays [11–13]. Cytokines may increase the permeability of the blood brain barrier and act on the hippocampus causing delirium and cognitive decline [13]. In colorectal cancer, high levels of inflammatory cytokines have been shown to promote malignant progression and recurrence after surgery [14]. Inflammation also compromises the mucosal barrier. This is pertinent to surgery as a compromised mucosal barrier exacerbates systemic inflammation secondary to bacterial metabolites, fragments, and possibly even intact bacteria getting into the systemic circulation [15]. There is evidence that prebiotics, probiotics, and synbiotics help enhance the mucosal barrier by several mechanisms [16].

If keeping inflammation at bay is the goal, one might ask what can be done to modulate the immune response? Consistent use of synbiotics, prebiotics, and probiotics has the potential to change our inflammatory status and may have implications in the perioperative period. In a recent study, 52 patients with colorectal cancer were given either a placebo or a probiotic supplement containing lactobacillus and bifidobacterium for 6 months after surgery. Patients in the probiotic group were found to have a significant reduction in levels of pro-inflammatory cytokines TNF-α, IL-6, IL-10, IL-12, IL-17A, IL-17C, and IL-22 [17]. In this study, Zaharuddin et al. observe that that IL-10 and IL-12 have somewhat of a dual functionality as anti-inflammatory and pro-inflammatory cytokines, but the study did not find a significant increase in uniquely pro-inflammatory cytokines with the use of probiotics.

The mechanism by which lactic acid producing bacteria (as in the Zaharuddin et al. study) exert an anti-inflammatory effect is unknown, although recent studies have elucidated possibilities. One example might be the activation of the vitamin D receptor autophagy signaling pathway [18], a pathway that may be associated with levels of IL-6 and other inflammatory cytokines [19]. There is also evidence that probiotics may affect inflammatory cytokine levels by acting on the NF-κB and MAPK signaling pathways [20, 21]. Of course, this is probably just the tip of the iceberg; mechanisms could be numerous and mixed and likely vary by species or even genus of bacteria. Prebiotics have also been implicated in several different anti-inflammatory pathways. These include reduction of pro-inflammatory cytokines and macrophages as well as the increase of regulatory T cells and anti-inflammatory cytokines [22–24].

Fermented foods are synbiotics which are often high in both prebiotics and probiotics, thus providing the immune modulating benefits of both groups. In fact, fermented foods may be a powerful tool to improve human health. In a recent study, Wastyk et al. randomized 36 adults to either a high fiber arm or a high fermented foods arm [25•]. Participants in the high fermented food arm consumed an average of 0.4 ± 0.6 servings per day of fermented food at baseline, which increased to an average of 6.3 ± 2.9 servings per day during the study. Yogurt and vegetable brine drinks were consumed at higher rates relative to the other types of fermented foods. These two fermented foods are largely

products of lactic acid fermentation, with analogous benefit to the lactic acid-producing bacteria administered in the colorectal cancer trial discussed above [17]. Wastyk et al. reported that microbiome alpha diversity (different types of bacteria) was significantly increased in the fermented food group, including new variants that were not present before the intervention. Microbial diversity has been correlated with human health [26, 27]. Although 90% of the bacteria in our microbiomes belong to just 20 species, the human microbiome has > 2300 species of bacteria that have been sequence [28]. The Wastyk et al. study demonstrates that in addition to an increase in microbiome diversity and introduction of new varieties of bacteria, several inflammatory markers decreased over the fermented food intervention, including IL-6, IL-10, and IL-12b [24]. These data support the anti-inflammatory findings of the probiotic and prebiotic data previously discussed and implicate fermented foods as a possible regulator of inflammation.

Beyond just reducing circulating levels of inflammatory markers in the blood, recent data utilizing a murine model demonstrate that kefir, a fermented milk synbiotic, alleviates tissue injury. In this study, mice were exposed to particulate matter by endotracheal instillation in order to induce pulmonary inflammation, oxidative stress, and overexpression of inflammatory markers. The lung tissue of the mice that were fed kefir had a reduction in oxidative stress and local inflammatory cell infiltration [20]. These data suggest that synbiotics may provide a systemic tissue healing benefit beyond the benefit to the local GI mucosa alone.

Although much of these data refer to the separate components, either prebiotics or probiotics, it does seem that the combination in the form of synbiotics and fermented foods may be of greater benefit than each component on its own. The anti-inflammatory nature of synbiotics provide an exciting potential therapeutic option to improve surgical outcomes.

Surgical and Hospital-Acquired Infection

Surgical site infection (SSI) is a potentially preventable cause of postoperative patient morbidity, and its occurrence contributes to increased healthcare costs. It is the leading cause of hospital readmission after surgery, approaching 20% of overall readmissions [29]. Surgeons and healthcare systems have increasingly focused on decreasing SSI rates through quality improvement initiatives and infection prevention bundles [30]. However, recent evidence has questioned the standard dogma that SSI results from intraoperative local contamination, but rather points to pathogens originating from sites remote from the operative wound [31]. Evidence against these long-held beliefs include studies demonstrating that > 80% of wounds with positive intraoperative cultures do not develop an SSI and wound cultures at the time of operation show no correlation with pathogens involved in the SSI [31]. Alverdy and colleagues have proposed a theory, termed the Trojan Horse hypothesis, whereby bacteria from the oral cavity or gastrointestinal tract can be taken up by immune cells and travel to the wound site, where they ultimately can cause an SSI [32]. Their team has been able to demonstrate this theory in a mouse model with fluorescence-labeled bacteria [32].

Given the above, is there a potential to alter the resident human oral and gastrointestinal microbiome to decrease wound infections following surgery? As already discussed in this review, administration of synbiotics can manipulate the composition of the gastrointestinal flora. Several randomized controlled trials (RCT) have employed synbiotics in abdominal surgery, with some trials demonstrating no difference when compared to placebo [33–35], but with the majority of studies demonstrating a benefit of synbiotics [36–45]. The trials have employed heterogeneous interventions, including probiotics only, probiotics plus fibers, and probiotics plus tube feeding containing fiber as well as various timing strategies with administration before, after, or both before and after surgery. Some trials have aimed to explore mechanisms, and many report effects on levels of inflammatory markers, as previously described, or on a decrease in pathogenic colonic bacteria (ref). Additionally, these trials have been combined as systematic review and meta-analysis, with the conclusion that synbiotics, specifically both before and after surgery, have the potential to reduce infectious complications significantly [46–49]. In the most recently published systematic review, including only RCT, there was an almost 50% reduction in postoperative infectious complications (RR 0.56, 95% CI 0.46–0.69; $P < 0.00001$, $I^2 = 42\%$) [46]. Finally, investigators in Japan have shown that perioperative oral care (professional oral care and oral self-care instruction) resulted in decreased risk of SSI compared to a control group (8.4 vs 15.7%, $P < 0.001$) [50].

Current meta-analysis suggests that synbiotics may also reduce the rate of respiratory, urinary tract, and wound infection complications following gastrointestinal surgery, in addition to shortening the length of hospital stay and antibiotic therapy, with no direct impact on mortality [51–57]. Newer data suggest that the use of preoperative plus postoperative synbiotics is more effective compared with only postoperative synbiotics or placebo, significantly reducing the incidence of infections, with less hospital stay and length of antibiotic usage [46, 58]. Synbiotics have also been associated with a greater benefit in reducing the incidence of VAP (RR 0.50, 95% CI 0.32–0.79) when compared to probiotics (RR 0.77, 95% CI 0.63–0.96) ($P = 0.09$) [51]: lower requirement for prokinetics, higher tolerance for tube feed administration, and decreased gastric residual volume (all $P < 0/05$) in critically ill patients [59].

Taken together, these data suggest that there is a potential benefit to perioperative administration of synbiotics for multiple types of abdominal surgery to decrease infectious complications. Administration both before and after surgery achieves the greatest benefit. Synbiotics are a relatively inexpensive intervention, which could result in fewer patients experiencing surgical infections and decreased healthcare costs. Results must be interpreted with caution as there is significant heterogeneity between studies and potential publication bias. Future studies should consider strain-specific evaluations to determine optimal formulations and consider ideal timing of the intervention.

Colorectal Surgery as a Model System for Host-Microbiome Interactions

Cancer Recurrence and Polyp Formation

Colorectal cancer is associated with advancing age, genetics, and environmental conditions, including dietary factors, smoking history, physical activity, antibiotic exposure, and alterations in the intestinal microbiome [60, 61]. Increasing research on the intestinal microbiome has identified a relationship between intestinal microbial dysbiosis, colon polyps, and colorectal cancer. Further understanding of how intestinal dysbiosis contributes to tumorigenesis may reveal ways to augment the microbiome to improve colon health.

Adenoma Formation Studies of the intestinal microbiome at the pre-neoplastic stage shed light on its relationship with the development of adenomas and progression to colorectal cancer. Recent evidence indicates that individuals with colorectal adenomas have distinctive microbiomes [62]. Watson et al. prospectively examined the microbiome of 104 individuals undergoing screening colonoscopies. Individuals were divided into adenoma and non-adenoma formers and oral, fecal, and mucosal microbiome samples were compared. They found that oral, fecal, and mucosal microbiomes are distinct. Specifically, they found that mucosal microbial abundances of adenoma formers have unique profiles, including specific taxa, that can reliably predict adenoma formation. Notably, oral and fecal abundances were not predictive of adenoma formation, suggesting that studies relying on fecal microbiome alone may be insufficient to characterize the intestinal microbiome, at least regarding adenoma formation.

Colorectal Cancer Recurrence Despite advances in treatment, colorectal cancer recurs in up to 38% of patients who were designated to have undergone a curable resection [63, 64]. Much of the focus on recurrence has been attributed to factors inherent to the tumor, including grade, stage, lymphovascular invasion, presence of obstruction or perforation, and post-residual tumor status after resection [65]. However, there is mounting evidence for the role of the intestinal microbiome in both colorectal cancer development and recurrence. Diet is well established as a factor in the intestinal microbiome composition and is further linked to colorectal cancer recurrence by evidence that individuals consuming a Western diet (WD), or a diet high in fat and low in fiber and prebiotics, have a higher risk of colorectal cancer recurrence [66]. Gaines et al. used a murine model to demonstrate that a WD promoted collagenolytic organisms and contribute to tumor formation after colorectal surgery [67•]. Mice were fed a WD versus standard diet (SD) for 4 weeks prior to surgery. Mice were given pre-operative antibiotics and underwent colon resection and anastomosis. Mice were given an enterococcus faecalis enema on post-operative day (POD) 1, followed by an enema of colon carcinoma cells on POD 2. Upon examining feces and colons on day 21, 88% of WD fed mice had peri-anastomotic tumors versus 30% of SD mice. Interestingly, tumor formation correlated with presence of collagenolytic *Enterococcus faecalis* and *Proteus mirabilis*, such that WD mice had threefold higher colonization. This experiment also employed a novel therapy, ± Pi-PEG, a non-absorbable polyphosphate that suppresses bacterial collagenase. In addition to antibiotics, Pi-PEG was provided in the drinking water of some mice. The investigators found that while antibiotics eliminated collagenolytic bacteria, they did not prevent tumor formation and, in fact, promoted emergence of collagenolytic candida parapsilosis. Conversely, WD fed mice given antibiotics, *E. faecalis* and Pi-PEG, had a statistically significant 57% reduction in tumor formation and maintained microbial diversity compared with control WD fed mice without Pi-PEG [67•].

It has been demonstrated that adenoma formers have distinct mucosal microbiomes.

Additionally, the evidence indicates that antibiotics, and dietary factors, specifically high fat and low fiber diet, induce intestinal dysbiosis and in certain instances promote microbes that disrupt anastomoses and contribute to colorectal cancer recurrence. Further understanding of these influences on the intestinal microbiome has the potential to impact outcomes related to colon polyps and colorectal cancer.

Anastomotic Leak

The reported rates of anastomotic leak (AL) vary between 1 and 19% in published data [68, 69]. Historically, tension, tissue perfusion, patient nutrition, and technique of anastomosis (stapled versus handsewn) are frequently investigated for causes of leaks. As our knowledge of the gut microbiome

has increased, so too has our understanding of its effects on outcomes following gastrointestinal surgery and the major role it may play in anastomotic healing. Anastomotic leaks are strongly associated with local colorectal cancer recurrence [70], and anastomotic environment seems to play a similarly important role in both cases.

Since bacteria colonize the mucosal surface of the bowel, the role of the mucosa should not be underappreciated when considering anastomotic leak. The resident microbial populations define the immune cells responsible for wound healing, such as the presence of M2 anti-inflammatory or "resolution" macrophages [71, 72]. Additionally, our current understanding is that the submucosa is composed of collagen and elastin, which provide the greatest tensile strength of all four layers of the bowel wall [73, 74]. Alverdy and colleagues again used a murine model to demonstrate that local microbial dysbiosis contributes to adverse surgical outcomes. They found that high abundances of *Enterococcus faecalis* and *Pseudomonas aeruginosa* play a critical role in the development of AL [75, 76]. In a mouse model, these bacteria contribute to AL's through collagen lysis by high collagenase activity and activation of matrix metalloprotease-9, which further degrades collagen [77]. The discovery of *Enterococcus faecalis* and protease activation is notable as this is the most common pathogen isolated in AL in humans [76, 78]. Both colorectal cancer recurrence and anastomotic leak are affected by collagenolytic bacteria in the anastomotic environment [67•, 75, 76].

These findings raise the possibility of targeting the gut microbiome to prevent AL. If the abundance and diversity of beneficial bacteria can be increased while reducing the abundance of those that promote collagen lysis, perhaps this can result in a strategy to reduce AL, though future mechanistic studies are needed. Hyoju et al. demonstrated in a murine model that anastomotic healing was improved in mice who were fed a low-fat/high fiber diet compared to mice fed with a WD. This group again found an increase in abundance of *Enterococcus faecalis* in both the lumen and stool in the WD group, which we have seen is collagenolytic [79]. In the case of both colorectal cancer recurrence and anastomotic leak, prebiotic pre-habilitation in murine models has shown to improve outcomes by altering the local microbiome [67•, 79].

Human studies have revealed mixed if not incomplete findings. The COLON study examined the association between habitual fiber intake and risk of complications after surgery for colorectal cancer in 1399 patients. Of the 1237 patients who had an anastomosis, 5% experienced an AL. Interestingly, higher dietary fiber intake was associated with a lower risk of any complication, defined as cardiopulmonary complication, surgical site infection (SSI), or post-operative ileus [80]. However, no association was found with AL [80].

In a randomized, double-blind, placebo-controlled study performed by Kotzampassi et al., patients undergoing colorectal surgery either received capsules of placebo or a four-strain probiotic formulation 1 day before surgery and continued for 15 days post-operatively. Of the 84 patients in the probiotics group, 1.2% developed an AL compared to 8.8% of the 80 patients in the placebo group. These findings were statistically significant, and the study was prematurely stopped due to the high efficacy of the treatment [81]. In addition, Veziant et al. performed a systematic review in 2022 analyzing 21 randomized control trials where 15 trials included probiotics and 6 evaluated synbiotics in patients undergoing colorectal surgery. While the pooled data did demonstrate significantly fewer infectious complications and SSI's, there was no difference seen for anastomotic leaks [82]. When analyzing the studies included, the studies varied in the timing of when the synbiotics/probiotics were given, there was heterogeneity in the formulations used, and doses varied.

Overall, the data linking the gut microbiome to AL are compelling though incomplete. While the exact physiology and mechanism underlying its association remain unknown, both Alverdy and the more recent clinical data are impressive. There appears to be a changing paradigm in the causal factors of AL and SSI, and microbiome-altering supplements may be a solution. More research using evidence-based synbiotic formulations is needed prior to widespread implementation.

Metabolic Syndrome

Epidemiologic data over the past few decades have shown that the host microbiome plays a crucial role in human health, including affecting the determinants of metabolic syndrome. This includes links to obesity, type 2 diabetes mellitus, cardiovascular disease, liver disease, and malnutrition. The increased risk for adverse surgical outcomes in patients with metabolic syndrome is well established. This suggests that altering the microbiome may be a powerful means to prevent adverse surgical outcomes related to metabolic disease by improving the physiologic response inherent with these comorbidities.

Patients with metabolic syndrome who undergo surgery have higher rates of death, cardiovascular events, coma, stroke, renal failure, and surgical site infections [83]. In addition to worse outcomes, these patients also experience prolonged hospitalizations, incur higher health service costs, and require more post-hospitalization care [84]. Although it is not realistic to alter the course of chronic diseases preoperatively, targeting the gut microbiome through dietary pre-habilitation may improve the immunologic response to surgery. Alverdy et al. have found

in various murine models that intestinal microbiota are altered and surgical outcomes are improved even with a short duration high fiber pre-habilitation diet when compared to a WD arm [67•, 79, 85•].

In addition, there is evidence in human studies which link the composition of the gut microbiome to metabolic syndrome. Data have shown that the composition of the gut microbiota differ between lean and obese individuals. For example, Tims et al. performed a study profiling the gut microbiome in monozygotic twins discordant for obesity and found that the species *Eubacterium ventriosum* and *Roseburia intestinalis* were positively correlated with higher BMI [86]. These species are associated with more direct butyrate production, as opposed to scavenging of fermentation products to form butyrate, which may negatively affect host energy harvest [86]. Evidence suggests the gut microbiome can affect host gene expression by altering the metabolic and inflammatory pathways along the gut-brain axis [87]. Vrieze et al. administered the microbiota from lean individuals into the small intestine of men with metabolic syndrome. After 6 weeks, insulin sensitivity increased in the recipients, where the rate of median glucose disappearance increased from 26.2 to 45.3 μmol/kg/min [88].

We see that the gut microbiome can impact determinants of metabolic syndrome, and metabolic syndrome leads to negative surgical outcomes. This begs the question, could microbiome-directed interventions in the form of synbiotics improve surgical outcomes? For example, studies using synbiotics in the form of fermented foods have shown improvements in certain markers of metabolic syndrome. Three different small studies, with remarkably consistent findings, used kimchi intake as the intervention. In all three cases, waist circumference and BMI were decreased. Additionally, decreased insulin resistance and decreased blood pressure were found with the kimchi intervention [89–91] Similarly, a double-blind, placebo-controlled trial was conducted in a cohort of children with obesity. These children were given one daily probiotics for 16 weeks and were compared to placebo. At the conclusion of the study, the group who received daily probiotics had a significant decrease in body weight, percent body fat, reduction in level of interleukin-6, serum triglycerides, and an increase in *Bifidobacterium* compared with controls [92].

Overall, there appear to be a growing body of literature implicating a favorable gut microbiome phenotype for metabolic health. Additionally, we know that metabolic syndrome can negatively affect surgical outcomes. This possible connection invites future studies to determine the extent to which synbiotics may have positive effects on surgical outcomes by altering aspects of metabolic syndrome.

Conclusion

In this review, we have examined the inflammatory effects of surgery and the importance of the host-microbiome relationship on surgical outcomes. Multiple studies have demonstrated a beneficial effect of synbiotics in the perioperative period to decrease multiple negative outcomes. Dr. John Alverdy is a leader in rethinking surgical dogma and investigating the impact of resident human intestinal bacteria on surgical outcomes. His group's work also suggests that even short-term gut microbiome pre-habilitation could alter surgical outcomes significantly. Future studies should consider evidence-based strain specific formulations and work to determine ideal duration of treatment. Additionally, dietary interventions, such as fermented foods and high fiber diets should be considered in perioperative regimens.

Data Availability The data that support the findings of this study are available upon reasonable request.

Compliance with Ethical Standards

Conflict of Interest The authors declare no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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