The Role of T-Cell Subsets in Chronic Inflammation in Celiac Disease and Inflammatory Bowel Disease Patients: More Common Mechanisms or More Differences?

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Key Words

Celiac disease · Crohn's disease · Cytokines · Microscopic colitis · T cells · Ulcerative colitis

Abstract

Background: Chronic intestinal inflammation due to noninfectious causes represents a growing health issue all over the world. Celiac disease as well as inflammatory bowel diseases (IBD) like Crohn's disease and ulcerative and microscopic colitis involve uncontrolled T-cell activation and T-cell-mediated damage as common denominators. Therefore, diagnosis and treatment decisions clearly benefit from the knowledge of the intricacies of the systemic and the local T-cell activity. **Summary:** Depending on the cytokine milieu, CD4⁺ T cells can differentiate into proinflammatory T helper 1 (Th1), anti-inflammatory Th2, antimicrobial Th17, pleiotropic Th9, tissue-instructing Th22 cells, and in the regulatory compartment forkhead box protein 3⁺ Treg, suppressive Tr1 or Th3 cells. Additionally, follicular Th cells provide B-cell help in antibody class switching; cytotoxic CD8⁺ T cells target virus-infected or tumor cells. This review discusses our current knowledge on the contribution of defined T-cell subpopulations to establishing and maintaining chronic intestinal inflammation in either of the above entities. It also puts emphasis on the differences in the prevalence of these diseases

between Eastern and Western countries. **Key Messages:** In celiac disease, the driving role of T cells in the lamina propria and in the epithelium mainly specific for two defined antigens is well established. Differences in genetics and lifestyle between Western and Eastern countries were instrumental in understanding underlying mechanisms. In IBD, the vast amount of potential antigens and the corresponding antigen-specific T cells makes it unlikely to find universal triggers. Increased mucosal CD4⁺ regulatory T cells in all four entities fail to control or abrogate local inflammatory processes. Thus, prevailing differences in the functional T-cell subtypes driving chronic intestinal inflammation in celiac disease and IBD at best allow some overlap in the treatment options for either disease.

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Introduction

Chronic intestinal inflammation clinically represents itself by frequent/recurrent vomiting, periods of (non-bloody) diarrhea and/or obstipation, abdominal pain, rectal bleeding, internal cramps and spasm, nausea, fever,

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Table 1. Prevalence of noninfectious chronic intestinal inflammation in different regions of the world

	USA	Europe	Asia
Celiac disease	710 [1]	1,000 [2]	<5 [3] ^a
CD	241 [4]	1.5–213 [5]	13.5 [6] ^a
UC	263 [4]	2.4–294 [5]	21.2 [6] ^a
Microscopic colitis			
Lymphocytic	39.3 [7]	~39.3 [8]	~39.3 [8]
Collagenous	63.7 [7]	~63.7 [8]	~63.7 [8]

Numbers of patients suffering from the condition per 100,000 persons are given. Data from most recent available references.

^a Japan only.

weight loss and overall developmental delay in children. With infectious causes excluded, celiac disease and inflammatory bowel diseases (IBD) represented by Crohn's disease (CD), ulcerative colitis (UC) and microscopic colitis cover the main range of diagnoses for the self-driving immune disorders. Differences in the genetic backgrounds, lifestyles and diet of the populations define the uneven distribution of these conditions throughout the world (table 1).

Celiac disease peaks at two different ages, usually setting on in early childhood after weaning or in the 4th decade of life [9]. Although it affects more women than men, the latter show more severe manifestations [10]. With the advent of screening methods, celiac disease is diagnosed in an increasing number of individuals without overt clinical symptoms [11]. Celiac disease is very rare in Japan, where rice is the staple food [3]. In contrast, celiac disease is frequent (about 1 out of 100 people) in Western countries [1, 2].

As for the main entities of IBD, CD and UC can manifest at any age, but the peak of onset is 15–30 and 20–40 years of age, respectively, with both sexes equally affected [12]. The onset of microscopic colitis occurs at late ages (50–60 years). Overall, it is rare and affects more women than men [13]. While CD and UC are about 10 times more frequent in Western than in Eastern countries, the prevalence of microscopic colitis, though overall rare, is similar in developed countries [7, 8].

These epidemiologic background data corroborate chronic intestinal inflammation as a major health issue. They also highlight that detailed knowledge of cellular mechanisms driving the diseases helps to understand the relative contribution of external and intrinsic factors leading to the different types of chronic intestinal inflam-

mation. T cells of various subtypes are deeply involved in initiating, maintaining and controlling chronic inflammation. We here thoroughly reviewed the literature searching for similarities and differences in celiac disease, CD, UC and microscopic colitis with respect to the T-cell compartments. We also addressed the contribution of established regional epidemiologic differences to our knowledge on T cell-dependent mechanisms.

Celiac Disease

By its dependency on defined antigens, celiac disease represents a prototypic CD4⁺ T cell-dependent disease with chronic intestinal inflammation. A strict diet free of wheat and other cereals that contain gluten consisting of glutenin and gliadin ensures absence of intestinal symptoms [14]. Histopathologically, celiac disease is diagnosed by severe crypt hyperplasia and villous atrophy in the small intestine [15]. Specific antibodies, primarily auto-antibodies directed at the tissue transglutaminase and antibodies directed at gliadin confirm the diagnosis [15, 16]. In persons genetically predisposed by the human leukocyte antigen (HLA) class II variants DQ2 ($\alpha 1^*0501$, $\beta 1^*0201$) and/or DQ8 ($\alpha 1^*0301$, $\beta 1^*0302$), CD4⁺ T cells recognize gluten-derived peptides that are deaminated by the tissue transglutaminase and effectively presented by the said HLA-DQ variants [17, 18]. Antigen-specific activated effector CD4⁺ T cells release proinflammatory cytokines, predominantly interferon- γ (IFN γ) [19] and interleukin-21 (IL-21) (fig. 1) [20]. Albeit crucial to initiate the immunopathology in the small intestine, various other T-cell subsets are involved in sustaining the heterogeneous cytokine milieu maintaining or counteracting the local inflammation. Besides gluten-specific CD4⁺ T cells within the lamina propria, intraepithelial lymphocytes (IEL) are massively increased and considered a hallmark of celiac disease [21–23]. These IEL are CD8⁺ T cells carrying the $\alpha\beta$ T-cell receptor (TCR) or CD4⁺CD8⁺ $\gamma\delta$ TCR⁺ T cells [24]. Innate IEL are drastically reduced upon intestinal inflammation in celiac disease [25, 26]. Both $\alpha\beta$ ⁺ and $\gamma\delta$ ⁺ IEL express NKG2D [27], a receptor recognizing self-proteins induced by stress, infection and transformation [28], while the inhibitory NKG2A receptors are downregulated [29]. NKG2D is upregulated by IL-15 produced by epithelial cells and the myeloid-cell compartment within the lamina propria [30, 31]. The oxidative stress in celiac disease [32, 33] leads to upregulation of the major histocompatibility complex class I chain-related protein A (MICA), the ligand for NKG2D, on epi-

thelial cells [34]. Hence, upregulation of NKG2D on IEL and the upregulation of MICA on epithelial cells results in IEL-mediated cytotoxicity of epithelial cells [35]. For induction of villous atrophy, the IEL must acquire a fully activated NK phenotype [29]. In celiac disease, IEL express high levels of IL-15R α binding IL-15 with high affinity [36]. In these IEL, IL-15 enhances production of IFN γ and tumor necrosis factor- α (TNF α) [30], induces proliferation [30] and has an antiapoptotic effect [37].

A small group of celiac disease patients do not respond to strict gluten-free diet and present with large numbers of aberrant IEL in a type 2 refractory celiac disease [38]. The abnormal cell phenotype includes the loss of surface CD3 with preservation of cytoplasmic CD3 ϵ [39, 40] and rearranged TCR γ chains [38, 41]. These abnormal and highly proliferative IEL are suggested to give rise to T-cell lymphoma [42], while others suggest innate IEL giving rise to enteropathy-associated T-cell lymphoma (EATL) [26, 43]. However, lymphoma in celiac disease patients is not confined to the EATL [44].

Besides its effect on IEL, IL-15 acts on other immune cells within the mucosa. It enhances IL-21 production in lamina propria lymphocytes (LPL) [45] and renders effector T cells resistant to suppression by forkhead box P3 (Foxp3)-positive regulatory T cells (Treg) [46]. Foxp3 is the master regulator of the development of Treg, which were first identified as CD4 $^{+}$ CD25 ^{high} T cells [47]. In humans, Foxp3 gene mutation also causes multiorgan inflammatory disease known as immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome [48, 49]. Treg also express high levels of IL-15R α and are increased in the lamina propria of celiac disease patients, where they are mainly located beneath the epithelium [36, 50]. So far, the cytokine profile of these mucosal Treg was never examined. It is likely that they produce IL-10 and transforming growth factor- β (TGF β) [51]. Early studies found normal IL-10 levels in the intestinal mucosa [32, 52]. Later, more sensitive approaches revealed increased levels of mucosal IL-10 mRNA [53]. As for the lymphocytes, IEL but not LPL are major sources of this IL-10 [54, 55]. Regarding mucosal TGF β production in celiac disease patients, LPL seem to be the main producers [56, 57]. Although mucosal TGF β seems to be inefficient in counterbalancing the proinflammatory milieu with IL-15 being a strong opponent, TGF β inhibits IL-2- but not IL-15-dependent T-cell proliferation [58, 59]. Additionally, low concentrations of TGF β in the presence of proinflammatory cytokines promote T helper 17 (Th17) differentiation [60]. Mucosal Th17 cells have been found in celiac disease [61–64], and elevated levels of IL-17A are associ-

Fig. 1. Aspects of T-cell-dependent interactions and mediators within the ileal mucosa in celiac disease. APC = Antigen-presenting cell; co = co-stimulatory signal; My = monocytic cell; tTG = tissue transglutaminase.

ated with late-stage disease when villous atrophy has developed [65]. The main producers of IL-17 are CD4 $^{+}$ and CD4 $^{+}$ CD8 $^{+}$ LPL [63]. The majority of these Th17 cells also produce IFN γ [63]. Gliadin-specific Th17 cells display functional plasticity playing a dual role as effector memory cells expressing CD45RO, the CC chemokine receptor 6, the natural killer cell receptor NKR-P1A and the IL-23 receptor [62]. They also produce proinflammatory cytokines (IL-17, IFN γ and IL-21) as well as the mucosa-protective cytokine IL-22 and regulatory TGF β [62].

All T-cell subsets involved in celiac disease seem to be antigen-specific: gliadin-specific CD4 $^{+}$ T cells [18], gliadin-specific Th17 cells [62], tissue transglutaminase-specific T cells [66, 67], antigen-specific IEL [68]. Gliadin might be recognized by cytotoxic CD8 $^{+}$ T cells due to epitope spreading [69].

Inflammatory Bowel Disease

CD and UC are the two main forms of IBD. CD is a chronic inflammatory disease that could involve the entire digestive organ, especially the small bowel and the colon, leading to the progressive destruction of the alimentary tract. Inflammation in CD observed in the mucosal, submucosal and muscular layers causes intestinal complications such as fistulae, perforation and stricture. Chronic inflammation in UC mainly affects the colon and rectum. Endoscopic and radiological examination reveals continuous and diffuse mucosal inflammation from the rectum to the proximal colon. In UC, fistula formation is relatively rare compared to CD, since the mucosal layer is a main target of inflammation. Another form of IBD, microscopic colitis, is mainly an inflammation of the large intestine, though the terminal ileum can be involved [70]. The term 'microscopic' refers to the fact that diagnosis demands microscopic examination. The patients suffer from chronic nonbloody diarrhea. On histology, lymphocytic and collagenous colitis appear as different entities [71, 72] that might be incorrectly grouped together [8]. In lymphocytic colitis, an increase in IEL to over 20 IEL counts per 100 enterocytes accompanies an architecturally normal colonic mucosa, a surface epithelial disarray and a mixed leukocytic infiltrate in the lamina propria [72–74]. Total IEL numbers are lower in collagenous colitis than in lymphocytic colitis [75]. Collagenous colitis shows an eponymous subepithelial collagen band of over 10 μm without alterations in the overall local lymphocyte counts [73, 76, 77].

In the local immunity of the intestinal mucosa, imbalances of T-cell subsets [e.g. Th1, Th2, Th17, Treg, natural killer T (NKT) cells] in the intestinal mucosa are hallmarks of IBD. The recent progress of research on the microbiota in mice has demonstrated that the intestinal flora can regulate T-cell differentiation [78–82], suggesting that dysbiosis may play a role in IBD pathogenesis.

Crohn's Disease

Before the discovery of Th17, the classical concept of CD as a Th1-dominant disease was widely accepted. Numerous studies demonstrate that lamina propria CD4⁺ T cells isolated from CD patients produce high levels of IFN γ (Th1). After the discovery of Th17 subsets, it has been reported that the IL-17-producing T-cell population (Th17) is also increased in the lamina propria of CD patients as well as Th1 cells. At present, dysregulation of the

innate immune system may trigger the onset of enhanced Th1- and Th17-acquired immune responses in CD. IL-12 and IL-23, mainly produced by dendritic cells and macrophages, play a key role in inducing the differentiation to Th1 cells. Indeed, mucosal IL-12 and IL-23 levels are elevated in CD patients [83, 84]. Dendritic cells from the mesenteric lymph nodes in CD generated Th1 and Th17 cells in vitro [85]. Abnormally activated intestinal macrophages in CD patients producing abundant TNF α , IL-6, IL-23 and TNF-like ligand 1A in response to commensal bacteria elicit an inflammation dominated by Th1 and Th17 cells [86–89]. The CD14⁺ macrophage subset is increased within the lamina propria of CD patients [88, 89]. CD14⁺ macrophages also possess an antigen-presenting function inducing both Th1 and Th17 cells [86]. Interestingly, CD14⁺ macrophages can induce a T-cell population producing IFN γ and IL-17 in vitro. Consistently, an IFN γ ⁺ IL-17⁺ T-cell population was observed in the intestinal mucosa of CD patients [90]. As for the plasticity in the T-cell development, this double-positive T-cell population is thought to differ from Th17 cells [91]. Colitis models in mice suggested a central role of the IFN γ ⁺ IL-17⁺ T cells in chronic intestinal inflammation [92, 93]. IL-21, mainly produced by activated CD4⁺ T cells and NKT cells, is required for Th17 cell differentiation, and the level of mucosal IL-21 is elevated in CD patients [94, 95].

IL-22 is a member of the IL-10 cytokine family that was recently discovered to be mainly produced by both adaptive and innate immune cells including dendritic cells, innate lymphoid cells, NK cells and CD4⁺ T cells. IL-22 regulates the intestinal immune status, especially enhancing barrier integrity and epithelial innate immunity. Among memory T cells, Th17 cells produce both IL-17 and IL-22. The novel T-cell subset Th22 produces IL-22, but neither IL-17 nor IFN γ . IL-22 produced by Th22 cells and innate lymphoid cells may play a beneficial role in human CD [96, 97].

Despite accumulating evidence from experimental colitis that mucosal Treg contribute to intestinal immune homeostasis and Treg dysfunction exacerbates colitis in mice, the role of Treg in human CD pathophysiology remains unclear. Treg in the human intestinal lamina propria were firstly identified as CD4⁺CD25^{bright} cells and were increased in the lamina propria of CD patients compared to normal controls [98]. The CD4⁺CD25^{bright} Treg numbers were higher in inactive than in active CD [99]. Immunohistochemical evaluation of mucosal Foxp3⁺ Treg corroborates the data from the periphery [99]. Treg accumulate in areas of active inflammation, including

Fig. 2. Aspects of T-cell-dependent interactions within the intestinal mucosa in IBD. APC = Antigen-presenting cell; co = co-stimulatory signal; MØ = CD14⁺ macrophage; TSLP = thymic stromal lymphopoietin.

granulomas and retain potent regulatory activity *ex vivo* [100]. Linking these Treg to Th17 cells in CD, the Treg population includes IL-17-producing cells [101, 102].

Ulcerative Colitis

In human UC, several studies of the mucosal cytokine profile, especially containing IL-4, IL-5 and IL-13, supported the hypothesis of UC as a Th2-associated inflammation [103–110]. As a histopathological characteristic of UC, mucosal IgG1⁺ plasma cell infiltration is observed, suggesting Th2 polarization. In addition, several studies demonstrated enhanced expression of Th2-associated cytokine such as IL-33 and thymic stromal lymphopoietin in colonic epithelial cells of UC patients, also suggesting a preference for Th2 polarization [111–115]. Other reports do not show Th2 polarization in UC [116–119]. The missing efficacy of type 1 IFN in clinical trials for human UC also contradicts the hypothesis of the Th2 dominance [120]. Since Th1 and Th2 cytokines are found in the inflamed colon in UC [105, 110], the Th1/Th2 balance may

vary depending on the severity and duration of the disease [105, 108]. Recently, several reports suggested enhanced production of IL-13 by mucosal NKT cells [121, 122]. IL-13 produced by mucosal NKT cells is a key cytokine in the pathogenesis of oxazolone-induced colitis, a Th2-dominant colitis model representing human UC also insofar as high numbers of nonclassical NKT cells producing IL-13 are found in the colonic mucosa [122–125]. IL-13 may play a role in the pathogenesis of UC by inducing epithelial cell damage [124, 126, 127]. Despite the accumulating evidence of IL-13 as a key molecule in a Th2-dominant mouse model of colitis as well as in human UC, anti-IL-13 therapy was not efficient in clinical trials with UC patients [128, 129]. Additionally, in the actively inflamed mucosa of UC patients, IL-22⁺ cells were reduced [130]. In 2014, a novel helper T cell subset expressing the transcription factor PU.1 and IL-9 consequently named Th9 cells was identified in patients with UC [131]. IL-9 is closely associated with autoimmune diseases, regulates the function of the intestinal epithelial barrier and therefore plays a role in the pathogenesis of UC [132] (fig. 2).

Recent studies have demonstrated that IL-17 also contributes to the pathogenesis of UC. IL-17 is expressed in the inflamed mucosa of UC patients [83, 106, 133, 134]. Like in CD, IL-23 from CD14⁺CD68⁺ macrophages promote Th17-cell immune responses crucially contributing to the chronic local inflammation of UC [135, 136]. Additionally, the T-cell population double positive for IFN γ and IL-17 and originating from Th17 cells is not specific for CD but also present in the intestinal mucosa of patients with active UC [90].

As for the regulatory T-cell compartment, increased Treg cells were also found in UC patients [98, 99, 137]. However, an IL-17⁺ Foxp3⁺ T-cell population in the peripheral blood of UC patients had impaired suppressive function *ex vivo* [138].

Microscopic Colitis

So far, little is known about the specifics of T-cell contribution to the course of microscopic colitis. It remains unclear whether local expansion or infiltration is responsible for an increase in T cells [71, 139]. Absent correlation between the severity of the clinical symptoms and IEL numbers or thickness of the collagen layer as characteristic features of the two entities points to a dominance of the inflammatory infiltrates in the mucosal lamina propria [140]. The LPL composition strongly depends on the disease state and the exact origin of the samples [141], which might help to explain differences in the T-cell compartment found in independent surveys.

Immunohistochemistry clearly showed CD8⁺ IEL locally increased in the colon tissue [142–145]. Defining them as effector T cells, these CD8⁺ IEL predominantly express the transcription factor T-bet [144]. Flow cytometry indicates that CD8⁺ cells within the LPL might be in fact memory cells double positive for CD8 and CD4 [139, 143]. Immunohistochemistry also revealed LPL single positive for CD4 [142, 144, 145]. About 60% of the CD4⁺ LPL were GATA-3⁺ [144] pointing to Th2 cells activated by TCR dependent or independent of the IL-4 receptor [146]. Treg counts are more increased in collagenous than in lymphocytic colitis [147]. In patients initially diagnosed with lymphocytic colitis that later developed collagenous colitis, overall IEL numbers dropped while Treg counts increased [147].

Although not specific for T cells, additional but indirect evidence for the contribution of defined T-cell populations comes from studies on the local inflammatory environment as defined by cytokines and chemokines. IEL in

microscopic colitis of both entities do not produce IL-15 [75]. Regarding mucosal cytokine production, mucosal mRNA of IFN- γ and IL-12/35 p35 was upregulated, while protein levels were not statistically significantly different [139]. Increased protein levels of IL-6 and TNF α were found in the mucosa of collagenous colitis but not lymphocytic colitis patients, while IL-21 was increased in both entities [139]. Immunohistochemistry also revealed increased IL-17 and IFN γ production [148]. Regarding Th2 cytokines, mucosal levels of IL-4, IL-5 and IL-10 were unaltered in microscopic colitis [139]. In the colonic mucosa of collagenous colitis patients, IFN γ , TNF, IL-17, IL-1 β and IL-6 but not IL-4 or IL-10 were found enhanced [149]. Chemokines and their receptors especially associated with CD8⁺ T cells in colon biopsies and overall low CD4⁺ T-cell counts, except for Treg, provide additional indirect evidence for a central role of CD8⁺ T cells in both entities [71].

Taken together, a closer look at the subgroups within the intestinal T-cell compartments in microscopic colitis might shed light on the sequence of inflammatory processes in individual patients and might clarify whether the types of microscopic colitis indeed are independent entities or if and under which conditions lymphocytic colitis also precedes the collagenous type.

Common and Different T-Cell-Dependent Mechanisms in Celiac Disease and IBD

The cytokines IL-17, IL-21 and IFN γ are increased in celiac disease and IBD, while an increase in IL-15 is only attributed to celiac disease. In celiac disease, antigen-specific CD4⁺ LPL and IEL (CD8⁺ and CD4⁺CD8⁺ $\gamma\delta$ TCR⁺) are the main drivers of the disease. Antigen-specific T cells might be critically involved in IBD too. Our lack of knowledge of defined antigens and the vast amount of potential candidates against the background of a variety of genetic dispositions renders it difficult to name common antigen-specific T-cell populations. The underlying assumption that individual combinations of antigens and presenting cells might be critical directs our hopes to the accessibility of high-throughput techniques. Although playing a role in microscopic colitis, IEL show no increased production of IL-15. Mucosal Treg are increased in celiac disease as well as in IBD. A specific Treg cell population also producing IL-17 in the mucosa of CD shows no impairment in regulatory capacity, while the suppressive activity of these cells was diminished in UC patients. As for microscopic colitis, Treg are more increased in lymphocytic than collagenous colitis.

In the past, CD was accepted as a Th1-dominated disease, while UC to be mainly mediated by Th2 cells. With the discovery of Th17 cells, it is acknowledged, that these cells contribute to the recurrent chronic intestinal inflammation in CD and that in UC Th1 cytokines are also increased. In microscopic colitis, Th1 cytokines are increased, while Th2 cytokines are unaltered. Also marking a difference in the IBD entities, Th22 cells are increased in CD but decreased in UC. Nothing is known so far about Th22 cells in celiac disease or microscopic colitis. The producers of IL-22 in the mucosa of celiac disease patients are Th17 cells. The hypothesis of altered Th1/Th2 or Th1/Th17 balance in the IBD pathogenesis seems very attractive. However, the mucosal immune status is more complex in IBD in humans than in inbred mouse models. Except for anti-TNF α and IL-12p40, targeting specific pro-inflammatory cytokines involved in the balance of local T-cell subsets in IBD treatment does not present promising additional therapeutic strategies yet. Clinical trials of both anti-IFN γ mAb (Th1) and anti-IL-17A mAb (Th17) in CD did not show significant efficacy [150, 151].

The role of Th17 in the pathogenesis of UC is also suggested in translational researches in patients treated with the anti-TNF α mAb infliximab. A subanalysis of the Ac-

tive Colitis Trial 1 revealed that the expression profiles of Th1-, Th2- and Th17-related cytokines in mucosal biopsy specimens were altered in the group of UC patients responding to the treatment with clinical remission [152]. The CD68⁺ macrophage-Th17 cell axis could be a therapeutic target for infliximab in UC as well as in CD [153, 154]. Infliximab has also been shown to be beneficial for patients with severe refractory celiac disease [155, 156]. For the treatment of diet nonresponsive celiac disease and refractory celiac disease, an IL-15 antibody is launched for testing in phase II by Celimmune. Microscopic colitis patients will require corticosteroid or immunosuppressive treatments, or even surgical intervention in refractory cases [157].

In conclusion, comparing T cell-dependent mechanisms in intestinal inflammation revealed more differences than similarities in the entities UC, CD, microscopic colitis and celiac disease.

Disclosure Statement

None of the authors has any potential financial conflict of interest related to this study.

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