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REVIEW

The Role of the Trace Element Selenium in Inflammatory Bowel Disease

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Abstract

One set of chronic gastrointestinal disorders called inflammatory bowel disease (IBD) is defined by persistent, non-specific inflammation. Abdominal pain, hematochezia, diarrhea, and other symptoms are among its clinical signs. Currently, managing and treating IBD remains a significant challenge. Patients with IBD frequently have deficits in trace elements. Selenium (Se) is one of the necessary trace elements for normal organismal function. It has several regulatory effects, including antioxidation, anti-inflammatory, and defensive properties, via inducing the synthesis of selenoproteins. Patients with IBD have been shown to have lower Se levels in epidemiologic research studies. Several experimental models of IBD suggest that Se or selenoproteins play a key role in microinflammation. We discuss the relationship between Se and IBD in this review, with an emphasis on a summary of potential mechanisms of action and applications of Se in IBD.

Keywords Inflammatory bowel disease · Selenium · Selenoproteins

Introduction

IBD, which encompasses ulcerative colitis (UC) and Crohn's disease (CD), is a chronic inflammatory illness affecting the gastrointestinal system. In the former case, symptoms include bloody diarrhea and fever along with abdominal pain; in the latter case, symptoms include fever, diarrhea, weight loss, and inflammation that can spread throughout the gastrointestinal tract. Although the exact cause of the disease is unknown at this time, the general consensus is that immune system alterations, intestinal microbiota, genetic host susceptibility, and other environmental and nutritional factors all play a role in its occurrence [1, 2]. Epidemiological studies have found that the incidence rate of IBD is increasing rapidly in the East, which is dominated by the newly industrialized countries, while it is stabilizing in the West, but the prevalence rate is still the highest in Western countries [3, 4]. Endoscopy is currently the primary diagnostic method for IBD; however, in severe cases, it might be challenging to distinguish between UC and CD [5, 6]. IBD is still an incurable medical condition as of right now. Despite the fact that biologics have revolutionized the way IBD is treated, some patients continue to exhibit clinical failure to respond [7]. Furthermore, using biological agents can have major negative effects like increased risk of cancer, autoimmune reactions, and severe infections. In recent years, novel anti-inflammatory medicines that target inflammatory pathways have been created with an updated understanding of pathophysiology. However, because there are currently only a few inflammatory pathways inhibited, a comprehensive therapeutic strategy has not yet been devised [8, 9]. IBD has a major negative influence on people's physical and mental health and quality of life, and its considerable rise in incidence around the globe has placed a significant financial strain on the state and society [10–12]. These negative effects continue to motivate the exploration of the mechanisms of IBD onset and progression as well as potential therapeutic strategies.

IBD is an inflammatory disease, and a number of studies have demonstrated the involvement of intestinal flora, oxidative stress, and macrophages in the inflammatory process

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of IBD [13–16]. Se has been gaining academic attention in recent years due to its anti-inflammatory and anti-oxidant properties and its ability to influence intestinal flora [17, 18]. Research has found that IBD is subject to micronutrient deficiencies, which are more common during the active period of the illness than during the remission phase. Often occurring deficiencies are those related to Se, ferrous iron, and vitamin D. The disease's severity and related comorbidities may worsen if these nutrients are deficient [19, 20]. Se, one of the essential trace elements, performs vital biological roles in the human body through selenoproteins, such as preventing oxidative damage, regulating immunity, inhibiting inflammation, and other areas [21, 22]. When a cardiomyopathy known as Keshan disease was first reported in China in 1935, supplementing patients living in endemic areas with Se was able to significantly lower the disease's incidence. This finding demonstrated the therapeutic potential of Se [23]. Se absence could lead to issues affecting various systems of the body, such as the conversion of thyroxine, male and female reproductive fertility, and the acceleration of HIV development [24, 25]. Supplementing with Se has anti-inflammatory benefits through regulating macrophage arachidonic acid shunting [26]. In addition, Se has a strong anti-oxidant capacity, which helps to significantly lessen the harm that reactive oxygen species (ROS) do to the intestinal mucosa. As our awareness of the connection between gut flora and IBD has improved, there is mounting evidence that Se may be involved in the development of the intestinal microbiota and, as a result, contribute to the effective regulation of inflammation [21, 27, 28]. This article explains the physiological roles of Se and how they relate to IBD, with a focus on the mechanism and function of Se in controlling intestinal inflammation. It also discusses the therapeutic uses of Se in IBD. As an outcome, this work offers a reference for a deeper look into the connection between Se and IBD.

Se and Its Physiological Functions

Se is present in every bodily tissue, although the liver and kidneys have the highest concentrations of the mineral. Se can enter the body through the digestive system from the outside and be used by it. Eventually, it is eliminated from the body through urine and feces [29]. Selenoproteins play a major role in the biological effects of Se. Selenoproteins exhibit varying substrate specificities and functions and are found in diverse organs and tissues. It is critical to preserving endothelial function stability, acting as an anti-oxidant and anti-inflammatory, preventing and combating cancer, maintaining the cardiovascular system, and improving brain function and neuronal activity [30].

To accomplish ideal effects and preserve human health, Se intake ought to be restricted within reasonable bounds. Excess of Se can result in acute and chronic toxicity, with cases that are severe possibly fatal [29]. Chronic overexposure to Se may raise the risk of Alzheimer's disease, hypertension, and pediatric leukemia [31]. Depending on events such as gender, age, or particular needs such as pregnancy and lactation, the National Academy of Sciences recommended different levels of Se. Men should take 40–70 μg of Se daily, and women should take 45–55 μg, established at 60–70 μg when breastfeeding or pregnant [32].

Correlation Between Se and IBD

IBD frequently ends in a Se deficit, and with advances in research, there is the recognition of the bond between Se and IBD. Nearly 30.9% of individuals with IBD are estimated to be Se deficient [17]. Deficits of such kind can exist even in periods of remission. It has been suggested that impaired intestinal absorption in patients is the primary cause of this phenomenon. Lower Se levels can also come with other factors, such as inadequate intake in the context of a restrictive diet, direct intestinal loss or hypercatabolic state in patients with IBD, and the use of drugs [33]. Se may be a non-invasive biomarker for determining the activity and severity of IBD since the degree of drop in serum Se levels in IBD patients correlates with the activity of UC and CD [34]. In a study, when Se was administered to IBD patients taking infliximab (IFX), they reported less severe side effects [17]. The protective effect of Se in IBD has been confirmed by experimental studies based on multiple models of animals [31, 35–37].

Role of Se in IBD

Se, Macrophages, and Arachidonic Acid

The immune system is one of the ways in which Se slows down the progression of IBD. It is well-established that the development of IBD is greatly mediated by the immune reactions of macrophages [14]. M1-type macrophage activation induces the release of numerous inflammatory substances (such as TNF-α, IL-1β, IL-6, IL-12, and IL-23), triggers the generation of ROS, and intensifies the inflammatory response. Conversely, M2-type macrophages that express CD206 and CD163 release anti-inflammatory molecules, including TGF-β and IL-10, which have the dual roles of aiding damage healing and acting as anti-inflammatory

agents [13, 38]. According to current research, Se can change M1-type macrophages into M2-type macrophages [17].

The ability of selenoproteins to effectively shunt the arachidonic acid pathway in macrophages represents the anti-inflammatory function of Se. The short version is that selenoproteins shunt the arachidonic acid pathway from producing more of the pro-inflammatory prostaglandin E2 (PGE2) to more of the anti-inflammatory prostaglandin D2 (PGD2) and its cyclopentenone metabolites [26]. Arachidonic acid is an essential fatty acid released from phospholipids in cell membranes and metabolized by the cyclooxygenase (COX), cytochrome P450 (CYP) enzyme, and lipid oxygenase (LOX) pathways [39]. Macrophages are capable of expressing a variety of receptors, and activation of these receptors occurs by mobilizing arachidonic acid in the phospholipid bilayer to produce lipid mediators. Arachidonic acid passes through the COX pathway to form PGH2, which is acted upon by a variety of synthetic enzymes, which in turn form specific prostaglandins that confer a variety of biological activities [40]. Selenoproteins are the primary means by which Se's biological actions are mediated, as was previously indicated. It was found that Se, in the form of the selenoprotein, upregulates the expression of hematopoietic prostaglandin D synthase (HPGDS), which in turn increases the production of PGD2 and its metabolite 15-deoxy-Δ-12,14-prostaglandin J2 (15d-PGJ2) [41, 42]. The latter is a member of the cyclopentenone prostaglandins (CyPGs) and, in conjunction with PGD2, both have strong anti-inflammatory properties [43]. More specifically, ① PGD2 generated with PGH2 has little to no substrate for PGE2, which is necessary for the start of an inflammatory response [40]. ② PGD2 and 15d-PGJ2 work together to adjust the balance of pro- and anti-inflammatory substances, and this serves to reduce inflammation by influencing leukocyte migration and macrophage efflux from the site of inflammation to the draining lymphatics [44]. ③ CyPGs have the ability to activate the nuclear hormone receptor peroxisome proliferator-activated receptor γ (PPARγ) and so initiate the anti-inflammatory process. Research on animals has revealed that CyPGs can stimulate the expression of HPGDS by binding to PPREs in the proximal promoter of mouse HPGDS, hence facilitating shunting [26]. Furthermore, the ability of 15-hydroxy prostaglandin dehydrogenase (15-PGDH), a NAD+-dependent dehydrogenase that aids in the catabolism of PGE2, to aid in the decrease of inflammation is improved by Se supplementation or PPARγ activation [43]. ④ CyPGs also have the ability to lower NF-κB activation [45]. It is believed that NF-κB plays a pivotal role in the immune response and functions as a fundamental modulator of inflammatory processes. When inactive, cryptic NF-κB dimers in the cytoplasm attach to the NF-κB inhibitory protein (IκB). Pro-inflammatory substances cause the IKK complex to become activated during an inflammatory response, degrading IκB and freeing NF-κB from IκB for nuclear localization. This process also increases the production of other pro-inflammatory factors [46]. CyPGs, a crucial component of IKK2 inhibition, prevent IκB from being phosphorylated and prevent NF-κB from entering the nucleus by reducing kinase activity [45]. Apart from the impact of CyPGs, Se also impedes the advancement of inflammation by blocking the separation of IκB proteins from NF-κB, which results in the suppression of NF-κB and diminishes its capability to release inflammatory mediators [26]. Furthermore, Se has the ability to increase IκB's normal half-life through modulating the activity of glutathione peroxidase (GPx) [47]. It follows that the exertion of the anti-inflammatory effects of PGD2, CyPGs metabolites, and PPARγ can be regulated by the involvement of Se and selenoproteins in arachidonic acid shunting in macrophages. Expression of selenoproteins in macrophages is critical for the protective effects of IBD (Fig. 1).

Anti-oxidant Properties of Selenoproteins

ROS are by-products of normal cellular metabolic activity and consist of oxygen radicals and non-radical compounds. (e.g., hydrogen peroxide (H_2O_2), hydroxyl radicals, lipid radicals, and (phosphorus) lipid hydroperoxides). Low and moderate amounts of ROS have beneficial effects on a variety of physiological processes, including killing of invading pathogens, wound healing, and tissue repair. However, excessive ROS production can pose a serious problem for body homeostasis and lead to oxidative tissue damage and even cell death [48, 49]. Normally, the body produces free radicals continuously, but with the support of anti-oxidants, it may protect itself from the damaging effects of ROS, maintaining a balanced ROS metabolism. The anti-oxidant defense system consists of enzymatic (e.g., superoxide dismutase (SOD), GPX, glutathione reductase (GR or GSR), catalase, and superoxide reductase) and non-enzymatic (e.g., glutathione, thioredoxin, and melatonin) mechanisms [49].

An imbalance between the generation and removal of ROS results in oxidative stress, which in turn causes the oxidation of proteins, lipids, and other biomolecules. The result damage to cell membrane structure and function, along with the production of inflammatory mediators, ultimately damages the intestinal mucosa and may be one of the primary mechanisms leading to the development of IBD [16, 50, 51]. The reasons for this outcome may be related to genetic susceptibility to oxidative stress, genetic variants, and environmental factors in IBD patients [50]. For example, Duox2 is a dual oxidase that releases H_2O_2 and affects gut microbes [52]. It was found that Duox2 is usually up-regulated in IBD, which leads to the production of excess H_2O_2, causing

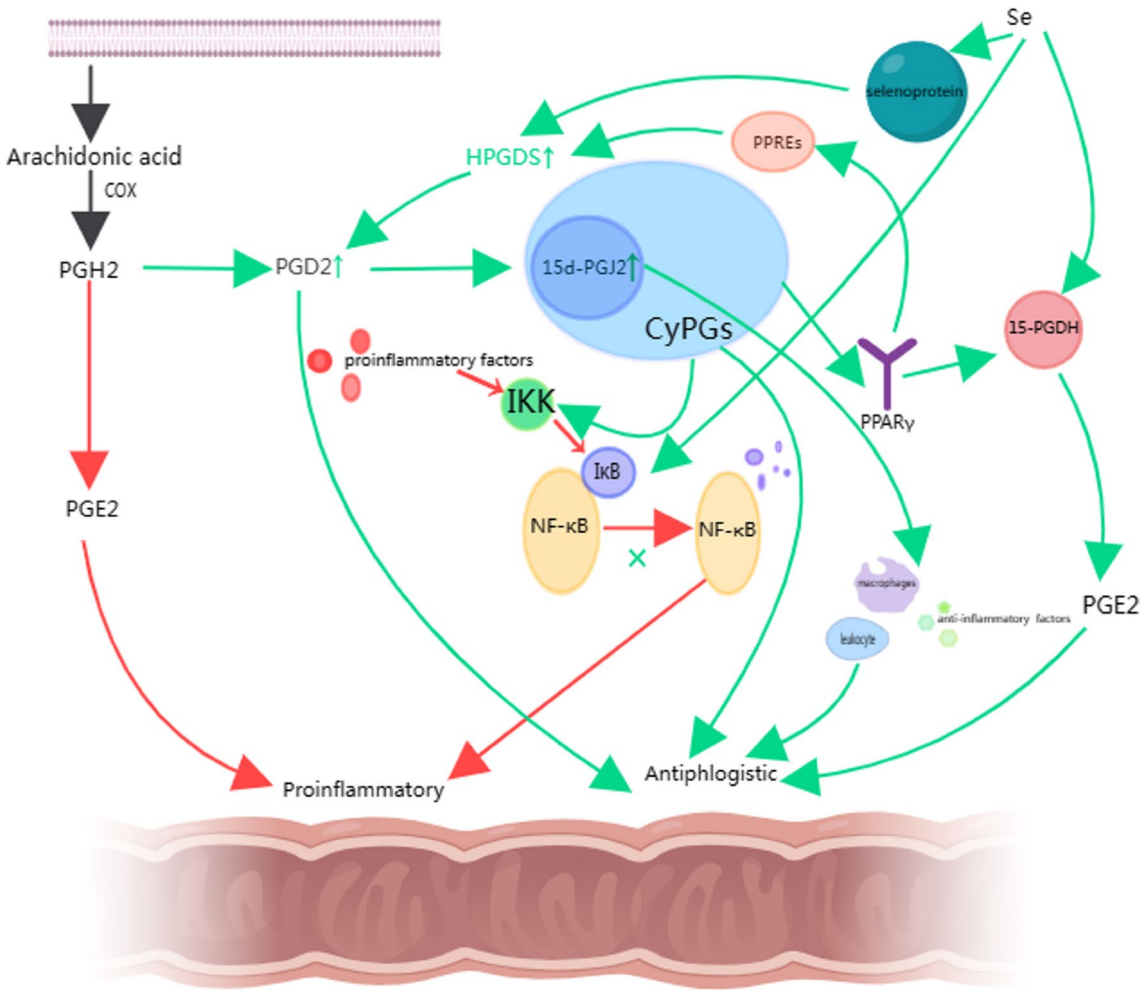

Fig. 1 Se mediates arachidonic acid shunting (Created with MedPeer (medpeer.cn))

intestinal mucosal damage [53]. Duox2 genetic variation has been shown in patients with early-onset IBD, in fact [54]. Nox1 is a NADPH oxidase that may play a part in inflammatory bowel disease (IBD) since it is abundantly expressed in the colon and its production is triggered by a number of pro-inflammatory mediators, including TNF-α, IL-1β, IL-18, interferon γ, and TLR5 ligand [55]. Nox1-derived ROS initiate and enhance the production of inflammatory mediators by colorectal cells [56]. We wonder if the Nox1-based oxidase system has a role in the pathophysiology of inflammatory bowel illness in light of this discovery. However, to date, little information is available in this regard. More research is needed in the future to understand how oxidative stress is specifically involved in the development and progression of IBD.

GPx is a vital anti-oxidant enzyme found in living things. It catalyzes the reduction process of hydroperoxides to water or corresponding alcohols, which preserves the equilibrium of ROS metabolism by scavenging excess hydroperoxides and shielding the organism from harm [48, 49]. There are several isoforms of GPx, an essential anti-oxidant enzyme that helps keep the body's ROS balance in check. The majority of these isoforms are dependent on Se. Interestingly, a Se shortage impairs the function of GPx but does not alter its creation [57]. Numerous research conducted recently have validated GPx's protective effect against alcoholic liver disease, allergic asthma, COPD, and other illnesses [51, 58–60]. Four isoforms of GPx are expressed in the gut; GPx1 activity is elevated in the colon and ileal crypts in an animal model of GPx2 knockout mice fed Se, corroborating the theory that it may play a partially compensating role. Furthermore, the loss of both GPx1 and GPx2 causes a strong inflammatory reaction that shows up as spontaneous ileocolitis [33]. Mainly expressed in the mucosal epithelium of the gastrointestinal tract, GPx2 inhibits PGE2 production that is dependent on COX2 and may therefore have anti-inflammatory effects in the gastrointestinal tract. It also links to the regulation of the equilibrium between intestinal cell

regeneration and apoptotic cell shedding. Mucosal tissues' essential extracellular anti-oxidant defense system, GPx3, is thought to be a tumor suppressor and is released by intestinal epithelial cells [40, 61]. GPx4 is a member of the selenoprotein family that is specific to catalyzing the reduction of oxidized biogenic lipids and can be expressed in the mucosa of the small intestine and colon [62]. The deletion of GPX4 results in tissue damage and sterile inflammation, which can cause or worsen IBD [63].

Furthermore, selenoproteins like selenoprotein W (SELENOW), selenoprotein P (SELENOP) have been shown to possess anti-oxidant and anti-inflammatory qualities. These properties have been shown to reduce oxidative stress, inhibit intestinal inflammation, and promote intestinal mucosal epithelial recovery during IBD. These findings highlight the anti-inflammatory and anti-oxidant potential of selenoproteins and the possibility of using Se supplements as an adjuvant therapy for IBD [26, 31, 64, 65].

Se and Host Microbial Colonization

Se may have an impact on the development and makeup of the gut flora, improving the health of IBD sufferers [64]. The term "intestinal flora" refers to the complex microflora formed by a variety of microorganisms in the human digestive tract. These microbes are strongly linked to the host's immunological response, nutritional status, and other physiological processes [68, 66]. Recent research has repeatedly shown that IBD patients have less overall diversity of gut flora, which results in an imbalance in the microbiota [64]. Even though the aforementioned circumstances might not immediately cause inflammatory events to occur, aberrant microbial colony structure and microbiota, including their metabolites, might influence intestinal permeability and immune function in the host, upsetting immunological homeostasis [67, 68]. More focused probiotic research and bigger controlled trials with transplants of fecal flora provide credence to this perspective [33, 69, 70]. It has been proposed that, on the one hand, gut microorganisms and the host are probably in a competitive struggle for resources. Conversely, however, Se levels also change the intestinal flora of the host, a finding supported by mouse experiments [40]. It has been documented that about a quarter of bacteria express selenoproteins, and therefore, they require Se for optimal growth. Microbial use of Se reduces the availability of this trace element for host selenoprotein expression. Furthermore, the capacity of different microbes to absorb, store, use, and eliminate Se varies [71]. This might contribute to varying gut microbiota compositions depending on the level of Se. Se supplementation may boost the intestinal tract's anti-oxidant capacity, boost immunity, and lessen the amount of damage caused by harmful bacteria to the intestinal tract, according to poultry experiments that suggested the possibility of protecting the flora [72]. Another study on animals discovered that by improving the intestinal barrier and changing the intestinal microbiota in mice, tea polysaccharides containing Se could lessen the symptoms of DSS-induced ulcerative colitis [73]. Regretfully, research on the affective qualities of Se on human gut flora is scarcer, and it is unclear if Se has a comparable impact on the makeup of human gut microbes. Based on the fact that Se deficit is common among IBD patients, it appears reasonable to test for Se deficiency and supplement Se to the gut flora of both IBD patients as well as healthy individuals. This will likely lead to new opportunities for both the avoidance and cure of IBD in the future.

Application of Se in IBD

The relationship between Se and inflammatory bowel disease (IBD) has been consistently highlighted in recent years, and due to the anti-oxidant and anti-inflammatory effects of Se, dietary modifications and pharmacological research involving Se have received attention [74–77].

Se, Diet, and IBD

One of the things impacting the onset of IBD is diet. According to one study, up to 89% of patients believed that dietary intake had the importance of preventing recurrence in managing their IBD, and 63% of patients thought that diet had a significant role in development associated with their IBD [78]. Nevertheless, there is not currently a comprehensive and trustworthy dietary guidance available. Based on insufficient data, 42 nations worldwide—including China, New Zealand, Europe, and Russia—are Se deficient. The positive aspect is that food provides the majority of the Se sources required by the body, so individuals may enhance and control their diets to meet the goal of Se supplementation [79].

Selenoprotein concentrations drop when there is a nutritional deficiency in Se. Se supplementation is known to affect selenoprotein expression. Following the ingestion of Se-rich foods, a randomized dietary intervention study conducted in Denmark discovered an enormous rise in SELENOP levels in the control group from week 13 to week 26 [80, 81]. One dietary pattern that may assist manage intestinal illnesses is the Mediterranean diet (MD). A high intake of fruits and vegetables (high in fiber, anti-oxidants, and vitamins), olive oil, oily fish (high in monounsaturated and polyunsaturated fatty acids), whole grains, and nuts are its defining characteristics [82]. Studies have found that MD

has benefits such as reducing inflammatory mediators, maintaining bone health, and reducing the risk of heart disease [83]. MD is a good source of Se as it advocates higher fish intake and can increase the position of Se in the diet [24, 84]. A prospective study found that following the MD for 6 months enhanced the quality of life for adult IBD patients by significantly reducing disease activity and improving hepatic steatosis and malnutrition-related indicators [85]. Although the study did not explicitly attribute the improvement in IBD to Se, given the anti-inflammatory and anti-oxidant properties of Se, an in-depth investigation of whether the MD can act as a "background therapy" for IBD by affecting Se levels in the body may be warranted. Furthermore, the effects of treatment modifications and subsequent effects of treatment prior to the dietary intervention on IBD were not entirely excluded in this study.

Se Preparations and IBD

There have not been many clinical studies looking into the therapeutic benefits of extra Se preparations for IBD patients. According to Maryam et al., those suffering from UC who took selenomethionine capsules orally for 10 weeks experienced clinical remission when compared to those who took a placebo capsule. Additionally, these patients had lower mean serum IL-17 concentrations and a lower mean score on the Simple Clinical Colitis Activity Index (SCCAI) ($P < 0.001$) [86]. In addition to having organic Se and probiotic efficacy, the usage of Se-enriched probiotics aids in the body's improved absorption of low-toxicity Se and has clear potential for controlling intestinal flora, anti-inflammatory, anti-oxidant, and other properties [87]. It has been discovered that se-enriched *Bifidobacterium longum* functions as an immunomodulatory and anti-inflammatory agent in ulcerative colitis produced by piroxicam and dextrose sodium sulfate (DSS) [88, 89]. The potential of nanomedicines to overcome the complicated milieu of the gastrointestinal tract and their high retention at the lesion site have garnered significant attention in recent years [90]. By controlling the overproduction of ROS, modifying the levels of inflammatory factors like TNF-α, IL-6, and IL-1 β in serum, and boosting the quantity of good bacteria and fatty acids with short chains, nano-selenium, or nano-Se, can effectively regulate the enteritis and improve intestinal function [91]. An experiment demonstrates that by improving the function of the intestinal mucosal barrier and anti-oxidant capacity, *Eucommia ulmoides* polysaccharide-modified nano-Se significantly relieved DSS-induced colitis [92]. Another animal investigation also demonstrated that nano-Se can significantly minimize oxidative stress [93]. This demonstrates the potential of nano-Se in the management of IBD. However, a great deal of study work still needs to be done because the key mechanisms in nano-Se relief of sickness are still unclear and the clinical investigation should be thorough.

Future Direction

Se is an essential element in the human body. Its level in the body is closely related to the normal physiological activities and functions of the body. Due to its anti-inflammatory and anti-oxidant qualities, Se may be crucial for the onset and development of IBD. More specific studies are needed in the future to elucidate the mechanisms underlying the effects of Se on IBD, with a view to providing more options for the treatment of IBD. Dietary patterns regarding Se are gradually improving the quality of life of IBD patients. The development and application of Se formulations have also provided new strategies for the treatment of diseases. However, in addition to the unclear mechanism of Se preparations such as nano-Se in alleviating IBD, attention should be paid to the dosage and safety of Se supplementation. Determining the right period of supplementation and the appropriate level of supplementation is key to treatment. In the future, a large number of basic and clinical trials are still needed to confirm the relationship between Se and IBD, which in turn will usher in a new turn in the prevention and treatment of IBD.

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Declarations

Competing Interests No potential conflict of interest was reported by the authors.

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