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Review

The Relationship between Gastrointestinal Health, Micronutrient Concentrations, and Autoimmunity: A Focus on the Thyroid

Michael Ruscio [1], Gavin Guard [1,*], Gabriela Piedrahita [2] and Christopher R. D'Adamo [2,3]

[1] Ruscio Institute for Functional Medicine, Austin, TX 94596, USA
[2] Nova Institute for Health, Baltimore, MD 21231, USA
[3] Department of Family & Community Medicine, University of Maryland School of Medicine, Baltimore, MD 21201, USA
* Correspondence: gavin@drruscio.com; Tel.: +1-360-622-6150

Abstract: Currently, there is a lack of understanding of why many patients with thyroid dysfunction remain symptomatic despite being biochemically euthyroid. Gastrointestinal (GI) health is imperative for absorption of thyroid-specific nutrients as well as thyroid function directly. This comprehensive narrative review describes the impact of what the authors have conceptualized as the "nutrient–GI–thyroid axis". Compelling evidence reveals how gastrointestinal health could be seen as the epicenter of thyroid-related care given that: (1) GI conditions can lower thyroid-specific nutrients; (2) GI care can improve status of thyroid-specific nutrients; (3) GI conditions are at least 45 times more common than hypothyroidism; (4) GI care can resolve symptoms thought to be from thyroid dysfunction; and (5) GI health can affect thyroid autoimmunity. A new appreciation for GI health could be the missing link to better nutrient status, thyroid status, and clinical care for those with thyroid dysfunction.

Keywords: gastrointestinal health; hypothyroid; nutrients; IBS; nutrient–GI–thyroid axis

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1. Introduction

The primary etiology of hypothyroidism is autoimmunity in Western populations where frank iodine insufficiency is not endemic. While many of these patients will require lifelong thyroid hormone replacement therapy, patients with subclinical hypothyroidism may improve their odds of not becoming frankly hypothyroid if nutritional therapy is administered.

Although many hypothyroid patients benefit from thyroid hormone replacement, a notable portion of hypothyroid patients (up to 40%) still struggle with symptoms despite being biochemically euthyroid when on thyroid replacement therapy [1–5]. As we will elucidate in further detail, evidence suggests that this may be secondary to interactions of what the authors have conceptualized as the "nutrient–gastrointestinal–thyroid" axis.

Integrative and functional medical care has greatly focused on how micronutrients are related to thyroid function. However, clinical care often misses a key therapeutic target of improving thyroid health and nutrient status; that is gastrointestinal (GI) health. Moreover, evidence is currently lacking in how thyroid health, nutrient status, and gastrointestinal health are interconnected with one another. A narrative review of human studies and existing review papers was conducted to investigate these potential interconnections of the nutrient–GI–thyroid axis for consideration in clinical care and future research.

2. Overview of Association between Thyroid Dysfunction, GI Dysfunction, and Nutrient Insufficiency

There is a wealth of research highlighting the often-overlooked connection between thyroid function, GI health, and nutrient balance.

An unexpected finding in 2017 concluded that being hypothyroid was the factor most highly associated with small intestinal bacterial overgrowth (SIBO), even more strongly

associated than intestinal surgery or acid suppression medication use [6]. A year later, Polish researchers found that SIBO patients had a higher likelihood of thyroid autoimmunity [7]. A randomized controlled trial published in 2019 then showed hypothyroid patients with residual symptoms had reduced TSH, required a lower dose of thyroid replacement hormone (Levothyroxine), and improved fatigue scores after 2 months of probiotics supplementation [8]. The latter finding may be due to probiotics' anti-inflammatory [9,10], anti-SIBO effects [11,12], and improved thyroid medication absorption [8].

Other GI imbalances are associated with autoimmunity, and thyroid autoimmunity in particular. For example, increased intestinal permeability markers are associated with a multitude of autoimmune conditions [13–17]. Specifically, intestinal permeability is found at higher rates in those with thyroid dysfunction and is associated with more thyroid symptoms [18]. In addition, a meta-analysis of 43 case-control studies showed that more virulent strains of *Helicobacter pylori* (*H. pylori*) can increase the risk of autoimmune disease including autoimmune gastritis and autoimmune thyroid disease [19].

This nutrient–thyroid–GI connection is also exemplified in a 2022 study suggesting 21% of autoimmune thyroid disease patients have anti-parietal cell antibodies (APCA) targeting the gastric mucosa [20]. As illustrated in Figure 1, the presence of APCA can predispose a patient to hypochlorhydria and subsequent key nutrient deficiencies, such as iron and B12. It has been shown that up to 4 in 10 hypothyroid patients are deficient in vitamin B12 which could contribute to "thyroid symptoms" such as fatigue [21].

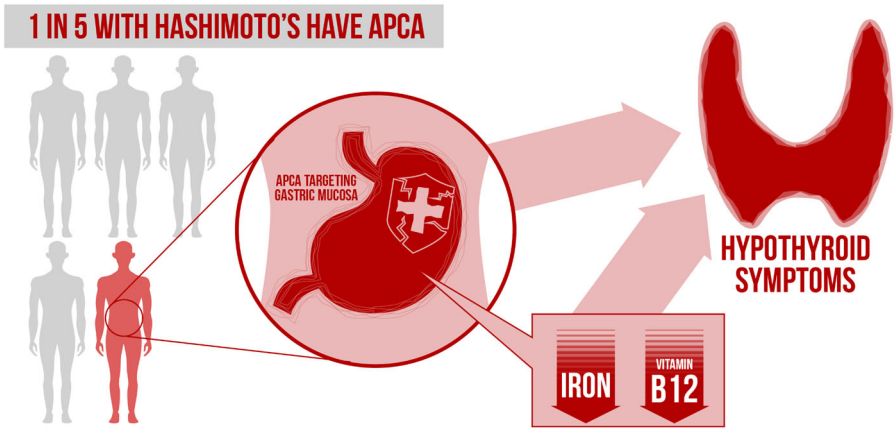

Figure 1. Relationship between Hashimoto's, parietal cell antibodies, nutrient deficiencies, and apparent thyroid symptoms.

An imbalance of one variable of the nutrient–GI–thyroid axis can lead to a downstream effect on the other parts of the axis.

2.1. Important Nutrients Required for Thyroid Health

A few select micronutrients, vitamins, and minerals have been proposed as essential for optimal thyroid function.

2.2. Iodine

Iodine is a non-metallic trace mineral that is an essential constituent of thyroid hormone synthesis and function. Iodine deficiency causes a variety of different disorders that include goiter and hypothyroidism. However, iodine is a double-edged sword for thyroid health; too much and too little are a problem. Iodized salt helps prevent goiter and other thyroid conditions. However, supplemental dietary iodine has also been shown to increase the incidence of thyroid autoimmunity [22–25].

In fact, a low-iodine diet can resolve hypothyroidism for a significant portion of people. In one study, over 75% of Hashimoto's patients who were assigned a low-iodine diet became euthyroid in 3 months [26]. Another study showed that 53% of hypothyroid

patients became euthyroid after just 3 weeks of iodine restriction. When iodine intake was resumed, they became hypothyroid once more [27].

Conversely, those following restrictive diets without adequate seafood or iodized salt intake run a risk of iodine insufficiency [28,29]. Thus, a proper balance of iodine is required for optimal thyroid function.

2.3. Selenium

Selenium is a mineral with antioxidant properties that plays essential roles in the function of the immune system and in metabolism of thyroid hormone. Supplementation has shown to be helpful for both hypothyroidism and hyperthyroidism. A meta-analysis of 16 controlled trials showed that supplementation for 3 months reduced TPO antibodies (−271 IU/mL, 95% CI [−366, −175], p-value < 0.0001) for patients who were also being treated with thyroid replacement [30]. Other studies have corroborated these beneficial results [31,32]; however, not all data agree [33,34]. While selenium has been shown to reduce TPO antibodies, to our knowledge, it has not been robustly studied to show a reduction in progression of disease.

On the other end of the thyroid spectrum, selenium reduced antibodies and the symptoms associated with Graves' disease [35]. Moreover, those with the highest serum selenium levels were associated with Graves' remission [36].

In addition, selenium may have a role in improving subclinical hypothyroidism and thyroid related symptoms such as depression [31,37,38]. These improvements may be maintained for months after just a short course of selenium supplementation [38].

2.4. Inositol

Inositol is a sugar involved in cellular signaling. Subclinical hypothyroidism can often be treated synergistically with both selenium and inositol [31,37,39,40]. Using these agents together may be more effective than selenium alone [41]. Inositol may work by improving the thyroid gland's sensitivity to TSH and lowering thyroid antibodies.

2.5. Vitamin D

Vitamin D is a secosteroid hormone that influences the expression of hundreds of genes. Low serum vitamin D levels are associated with hypothyroidism [42,43]. Treatment with supplemental vitamin D shows a large beneficial effect for reducing thyroid antibodies (both TPO and Tg antibodies) [44]. However, at least 3 months of treatment may be required to see a notable effect.

2.6. Iron

Iron is a trace mineral that has an essential role in human development, oxygenation of the blood, and production of hormones. Iron deficiency may be a key reason why some hypothyroid patients remain symptomatic. In fact, up to 50% of hypothyroid patients who are symptomatic despite thyroid replacement therapy have iron deficiency [45]. When hypothyroid women with persistent symptoms, despite appropriate levothyroxine therapy, increased their serum ferritin levels to greater than 100 mcg/L with iron supplementation, two-thirds of them had resolved fatigue [46].

It has been proposed that iron deficiency can significantly worsen thyroid function, including [47]: increase the risk of positive TPO antibodies, increased TSH, decreased fT4, and increased prevalence of overt and subclinical hypothyroidism.

Iron deficiency often has GI etiology as we will discuss later (e.g., gastritis, celiac disease). Thus, iron deficiency is a key variable in managing cases of thyroid dysfunction, especially when patients are symptomatic despite adequate thyroid replacement.

2.7. Vitamin B12

Vitamin B12 is a water-soluble vitamin with critical roles in metabolism, methylation, and function of the nervous system. As stated earlier, up to 40% of hypothyroid patients

have B12 deficiency [21]. Another study found that lower B12 and vitamin D levels were correlated with more TPO antibodies in a dose-dependent manner [48]. A third study showed that those with autoimmune thyroid disease had about 50% the B12 levels as healthy controls (200.70 vs. 393.41, *p*-value <0.0001) and was inversely correlated with TPO antibodies [49].

2.8. Zinc

Zinc is a mineral that is a component of hundreds of enzymes in the human body, exerting broad activity on the immune system and the production of a variety of neurotransmitters and hormones. While zinc has been proposed as a thyroid-supporting nutraceutical, some [50,51], but not all [52], studies show that zinc levels are associated with thyroid function. Thus, more research is needed to clarify supplemental zinc's role in improving thyroid function.

2.9. Magnesium

Magnesium is a mineral and cofactor for hundreds of enzymes that is involved in energy production, cell signaling, and DNA synthesis. Magnesium may play multiple roles in thyroid function including having an anti-inflammatory effect and reducing thyroid antibodies [53]. Magnesium deficiency is associated with higher thyroglobulin antibodies and hypothyroidism [54]. In addition, magnesium supplementation can improve symptoms attributed to thyroid dysfunction (e.g., fatigue, cognitive function, and constipation) [55–57].

Furthermore, one small case series found combined nutraceutical supplementation including magnesium improved thyroid function, reduced antibody titers, and led to normalization of thyroid ultrasound morphology in the majority of cases [58]. While this is merely one data point in a small cohort of patients, it suggests that a multiple-nutrient intervention could be used in clinical practice.

3. Impact of GI Conditions on Status of Micronutrients Important for Thyroid Health

Many imbalances of the GI ecosystem have been found to directly impact the levels of the aforementioned key micronutrients important for thyroid health.

3.1. Gastritis

Gastritis is inflammation of the gastric secondary to some form of gastric injury. It is often caused by an infection (e.g., *H. pylori*) or immune-mediated (autoimmune gastritis). Gastritis (either *H. pylori* or autoimmune) is associated with a deficiency of vitamin B12 and iron [59,60]. This can then lead to anemia and symptoms thought to be from thyroid dysfunction (i.e., fatigue, depressed mood).

3.2. Irritable Bowel Syndrome (IBS) and SIBO

IBS is a functional GI disorder that is characterized by abdominal discomfort with associated changes in stool frequency and/or consistency. It is a multi-factorial process often involving microbial alterations, immune system changes, gut–brain dysfunction, mast cell reactivity, food sensitivities, altered motility, visceral hypersensitivity, and possibly inflammation.

IBS and SIBO are associated with deficiencies of vitamin D [61,62], vitamin B12 [63], and serum zinc [64].

Furthermore, anxiety around foods that can trigger IBS symptoms can lead to avoidance of many nutrient-rich foods. This was exemplified in a recent cross-sectional analysis of 950 IBS patients that found that 13% exhibited severe food avoidance [65].

3.3. Inflammatory Bowel Disease (IBD)

IBD encompasses two distinct autoimmune conditions, ulcerative colitis (UC) and Crohn's disease (CD). UC only affects the colon and inflammation is localized to the mucosal layer. CD can involve any part of the GI tract (anus to oral cavity) and involves transmural inflammation. IBD patients are at risk for malnourishment, increased catabolism, and reduced dietary intake which can compromise nutrient status [66]. Similar to IBS, those

with IBD may exhibit food avoidance behavior. A systematic review of 19 studies found that active IBD patients consume less vitamin B12 as compared to healthy controls (less than 50% of recommended dietary intake) [67].

Furthermore, rates of zinc and selenium deficiency were more common in Crohn's disease patients (selenium 15%, zinc 60%) compared to ulcerative colitis patients (selenium 6%, zinc 52%) and controls (selenium 0%, zinc 37%) [68]. This could be secondary to Crohn's disease affecting the small intestine which is the main source of nutrient absorption.

3.4. Celiac Disease

Celiac disease is an autoimmune condition of the small bowel triggered by gluten consumption that can lead to villous atrophy, mucosal inflammation, and crypt hyperplasia. It can lead to atrophy of the small intestine microvilli and is associated with impaired iodine absorption [69]. In addition, up to 50% of celiac disease patients are iron deficient at the time of diagnosis [52].

3.5. Proton Pump Inhibitor (PPI) Use

PPI medications such as omeprazole and esomeprazole exert an effect by suppressing gastric acid secretion by inhibiting the H+/K+-ATPase in the gastric parietal cell of the stomach. Patients with iron deficiency taking PPIs can have suboptimal responses to iron supplementation [70]. PPI use is also associated with decreased zinc absorption [71] and lower serum B12 [72]. This may be secondary to an iatrogenic state of hypochlorhydria impairing the absorption of these key nutrients.

3.6. Exocrine Pancreatic Insufficiency (EPI)

Finally, EPI is a condition whereby the pancreas produces a relative lack of enzymes necessary for proper digestive function, often a result of chronic pancreatitis. Those with EPI had a much higher rate of micronutrient deficiencies compared to health controls (42% EPI, 6% controls) [73]. The most common micronutrient deficiencies include those important for thyroid function such as selenium and magnesium. EPI may also predispose an individual to vitamin A and vitamin D deficiencies [74].

In summary, conditions affecting the GI system can result in frank and subclinical deficiencies of important nutrients important for thyroid function.

4. GI Therapies Can Improve Nutrient Absorption

Fortunately, a number of minimally invasive GI therapies have been found to improve status of nutrients involved in thyroid function.

4.1. Probiotics

Probiotics are considered to be live microorganisms that may elicit a health benefit on the host. Probiotics may improve nutrient absorption and micronutrient status. For example, a systematic review of 14 studies found that intake of probiotics in healthy subjects was associated with a beneficial impact on micronutrient levels including vitamin B12, calcium, folate, iron, and zinc [75]. Another clinical trial showed improvement in plasma B12 and homocysteine levels after 40 days of probiotic-infused yogurt intake [76]. The same study also showed a marked decrease in anemia rates.

The addition of synbiotics to iron supplementation led to greater iron levels [77]. This beneficial effect on iron status has been replicated in other studies [78,79]. Furthermore, probiotics have been shown to improve eradication of *H. pylori* [80,81] which is associated with gastritis and thus, impaired nutrient absorption.

4.2. Elemental Diet

An elemental diet is a meal replacement formula of pre-digested protein and carbohydrates that is absorbed in the first few feet of the small intestine. It has shown a drastic reduction in global malnourishment rates. This was highlighted in a clinical trial

of 144 Crohn's disease patients who used a semi-elemental diet. After 4 months of therapy, the rate of those who were moderately or severely malnourished decreased from 91% to 24% [82]. An earlier 1995 trial showed an improvement in iron status after 4 weeks of elemental dieting in 19 patients with Crohn's disease [83].

4.3. Immunoglobulins

Serum-derived immunoglobulin/protein isolate (SBI) is a compound that binds to allergens and antigens, including bacterial toxins in the gut that renders them less able to irritate the gut mucosal lining and stimulate the immune system. The use of immunoglobulins in refractory IBS patients may improve nutrient absorption by reducing intestinal permeability [84,85]. Presumably, these benefits are secondary to improved dysbiosis and intestinal permeability, but more research is needed to clarify the exact mechanisms behind these findings.

In summary, many key nutrients are vital for proper thyroid function (Figure 2). Multiple GI imbalances can lead to impaired absorption of these nutrients. Fortunately, GI care may lead to improved absorption of these nutrients which could indirectly affect thyroid health.

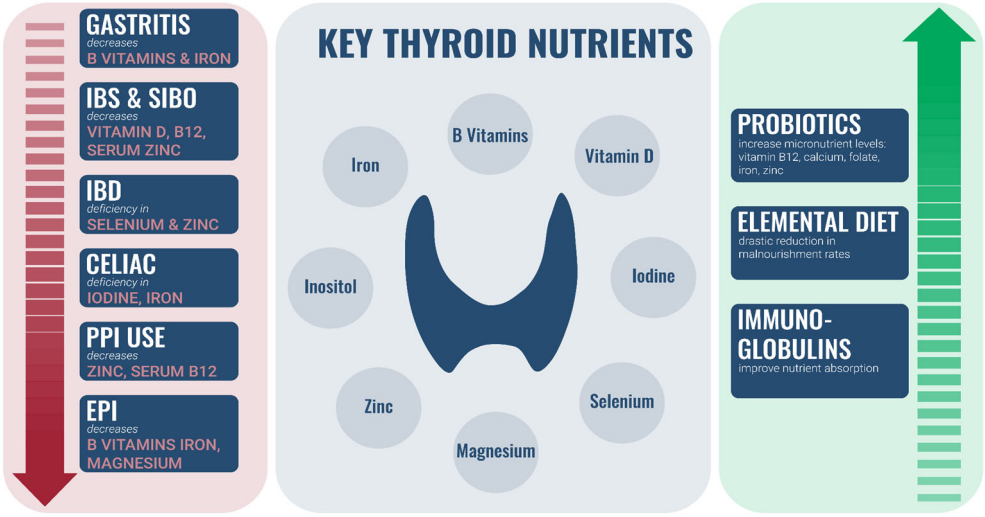

Figure 2. Relationship between nutrients, GI dysfunction, and GI-focused care.

5. Are Symptoms Emanating from the GI Tract or Thyroid?

The research provides compelling examples of how GI dysfunction causes thyroid-like symptoms. Seemingly challenging thyroid cases have been resolved by a GI-focused care model as noted in the research team's previous published case series and literature review [86]. For example, a woman with long-standing hypothyroidism and multiple thyroid medication changes floundered in 15 months of thyroid-focused care. It was not until she started on a foundational GI protocol consisting of triple probiotic therapy, herbal antimicrobials, and intestinal repair nutrients that her symptoms resolved and her thyroid function (TSH, fT4, TPO antibodies) improved.

The overlap of thyroid and GI symptoms is evident from the data. The five most common thyroid symptoms with the best predictive value of hypothyroidism include fatigue (81%), dry skin (63–76%), cold intolerance (64%), mood imbalance (46%), and hair loss (30%) [87,88].

However, these "hypothyroid symptoms" can also be from poor GI health. For example, IBS has been associated with fatigue [89,90], worse quality of life [91], depression [92,93], anxiety [94,95], and sleep disturbances [89,95,96]. SIBO has also been associated with both depression and anxiety [97].

In addition, other examples of GI imbalances leading to symptoms thought to be from thyroid dysfunction include the fact that non-celiac gluten sensitivity (NCGS) is associ-

ated with fatigue [98–100] alongside both anxiety and depression [98,99,101]. Moreover, malabsorption in IBD is associated with abnormalities of skin, hair, and nails [102,103].

The collection of above data supports the hypothesis that many symptoms attributed to thyroid dysfunction could in fact, be secondary to covert disturbances in the GI.

6. GI Care Can Resolve Symptoms Thought to Be from Thyroid Dysfunction

There are multiple lines of evidence that apparent hypothyroid symptoms (fatigue, depression, constipation) can be ameliorated with GI therapies.

Low FODMAP diet improves pain, anxiety, and quality of life [104–106]. Probiotics can improve depression and anxiety [105,107–111], cognitive function [112–114], SIBO eradication rate [7–9], and depression in those with SIBO [115]. Elemental diet improves quality of life [116,117]. Rifaximin improves cognitive function [118–120]. Improving intestinal permeability reduces chronic fatigue [121]. Fecal microbiota transplant improves fatigue and quality of life [122].

Multiple theories can explain the findings of GI therapies improving "thyroid symptoms". These include: the symptoms were actually from GI imbalances, and not from thyroid dysfunction (as we will cover below); lower inflammation; modulation of the GI–brain axis; improvement of nutrient absorption; histamine intolerance which affects up to 43% of those with digestive disorders and can mimic hypothyroid symptoms [123]; and GI therapies improved absorption of thyroid medication.

It is clear that GI dysfunction can cause thyroid-like symptoms, and more importantly, GI treatments can resolve these same symptoms. We should also ask, "How likely is a clinician to see this presentation in their patients and what does the prevalence data suggest?". Fortunately, there are compelling epidemiological data that address this question.

7. GI Dysfunction Is at Least 45 Times More Common Than Hypothyroidism

Frank hypothyroidism affects about 0.3% of the population [124–127] whereas IBS affects around 15% [128–130]. However, only about 30% of IBS cases are diagnosed [131], so IBS is likely more common than 15% of the population. It is important to note that some studies report much higher rates of hypothyroidism, but this is often reporting subclinical hypothyroidism which affects roughly 4% of the population [124–127]. Still, functional GI disorders such as IBS still affect a higher prevalence of the population.

Therefore, a conservative estimate puts IBS as 45 times more common than frank hypothyroidism. Clinicians are thus considerably more likely to see cases of GI dysfunction than they are of overt hypothyroidism. In the absence of lab-confirmed frank hypothyroidism, the cause of symptoms such as depression and fatigue are more likely a result from GI imbalances than from thyroid dysfunction. The higher prevalence of GI dysfunction is further compounded by overdiagnosis of hypothyroidism, detailed below.

8. Hypothyroidism Is Incorrectly Diagnosed and Overdiagnosed

A growing trend in medical care is attempting to achieve "optimal" thyroid levels, sometimes through the means of prescribing thyroid replacement therapy. However, many hypothyroid patients are likely incorrectly diagnosed. As many as 61% of hypothyroid patients with a history of an ambiguous initial diagnosis can successfully discontinue medication and remain biochemically euthyroid with a majority reporting an improvement of their symptoms [132]. Another study found that two-thirds of patients started on levothyroxine had subclinical hypothyroidism where the mean TSH level at the initiation of treatment was 5.3 mIU/L [133].

This is important because many with subclinical hypothyroidism do not benefit from medication and have TSH normalize with time. This was highlighted in a study of 225 subclinical hypothyroid patients, where 74% had normal TSH at a 6-month follow up without any intervention [134]. A larger study of 422,000 people found that 62% of those with TSH between 5.5–10 had a normal TSH at a 5-year follow-up [135]. This is why the European Thyroid Association recommends a repeat TSH after 2–3 months in most cases of

mild subclinical hypothyroidism [133]. This practice would likely lead to less individuals prematurely placed on unnecessary life-long thyroid medication.

Moreover, there is a trend in the evidence that there is a lack of benefit for treating elderly individuals with subclinical hypothyroidism if TSH is below 7–10 mIU/L [136–140]. This may be because TSH naturally rises with age and could be considered as a normal anomaly that does necessitate treatment [140].

Third and finally, research has revealed that many patients do not need lifelong thyroid medication. Another meta-analysis found that 37% can successfully discontinue their medication and remain biochemically euthyroid even after a 5-year follow up [141]. This could mean that some individuals were likely placed on thyroid replacement medication either prematurely or inappropriately. The trend of incorrect and overdiagnosis of hypothyroid has led many clinicians and researchers to overlook GI health.

9. GI Therapies Improve Exogenous Thyroid Hormone Absorption

Improving one's GI health may be a pivotal part of improving thyroid medication absorption and should be considered before attempting to fine-tune thyroid type (i.e., desiccated, combo T4/T3) [142].

For example, probiotics have been shown to reduce TSH, reduce the required levothyroxine dose, and improve fatigue levels in hypothyroid individuals who were symptomatic despite appropriate Levothyroxine therapy [8]. Similarly, three studies have now shown that treating *H. pylori* improves TSH levels and may reduce required levothyroxine dose [143–145].

While there are no robust clinical trials on the SIBO-thyroid medication association, a recent case study sheds light on this powerful potential therapeutic target. A case study published in 2021 of a 51-year-old female with long standing Hashimoto's and multiple food and medication sensitivities failed to achieve proper TSH balance over the course of 6 months, despite multiple medication changes (general T4, brand T4, combined T4/T3). It was not until she switched to a liquid T4 and then treated SIBO with rifaximin, that she achieved euthyroidism and resolved her symptoms [146]. Similar successful results were documented in the authors' recent case series [86].

Clinicians may also find success by addressing potential food intolerances/sensitivities to improve thyroid medication malabsorption. Lactose intolerance is found in 76% of hypothyroid patients [147]. After 8 weeks of a lactose-free diet, a lower TSH was achieved in both euthyroid and subclinical hypothyroid participants. Similarly, a gluten-free diet leads to less necessary levothyroxine dose in those with atypical celiac disease [148].

Finally, proper output of hydrochloric acid is necessary for optimal thyroid replacement absorption. Studies have found that patients with impaired stomach acid secretion require higher doses of levothyroxine medication [144,145]. In a prospective study published in the New England Journal of Medicine, 10 patients with stable TSH started taking a PPI [145]. This led to a 37% increase in the median levothyroxine dose needed to maintain normal TSH levels.

In light of these findings, it can be deduced that improving GI health (especially gastric and small bowel health) can improve thyroid medication absorption and thus, lower the need of medication to maintain euthyroidism in many patients.

10. Impact of GI System on Autoimmunity and Thyroid Autoimmunity

Imbalances of the GI ecosystem can directly and indirectly affect the immune system and are associated with states of autoimmunity, including thyroid autoimmunity [149]. As stated before, *H. pylori* is associated with multiple autoimmune conditions [19]. In addition, *Yersinia enterocolitica* was associated with a 4.3 times higher rate of thyroid autoimmunity [150], especially Graves' (odds ratio 6.1, 95% CI [3.71–10.10], $p < 0.0001$). Other studies found that Graves' and Hashimoto's patients have higher rates of Yersinia IgG and IgA antibodies [151,152]. In addition, a systematic review found SIBO was present in 39% of patients with systemic sclerosis and associated with an average of 3.7 years longer disease duration [153].

The connection between GI health and autoimmunity may be mediated by increased intestinal permeability [13–17] caused by various forms of GI imbalances (i.e., SIBO, dysbiosis, pathogens). One study found that increased GI permeability is found at higher rates in those with thyroid dysfunction and is associated with more thyroid symptoms [18]. A small pilot study found that children with Hashimoto's disease have increased markers of leaky GI when compared to controls [13]. In this study, higher serum zonulin was associated with higher levothyroxine dose. In other words, more intestinal permeability was associated with more thyroid dysfunction.

Similarly, higher GI permeability levels among Graves' patients were associated with higher antibody levels, lower TSH, higher fT4/fT3, and more symptoms [18]. This suggests that dysbiosis and intestinal permeability have a direct interaction and impact on thyroid autoimmunity (both Hashimoto's and Graves' disease) and can contribute to the autoimmune phenomenon as a whole.

GI therapies directly reduce autoimmunity, suggesting that GI health may be a root cause behind the pathogenesis of autoimmunity. For example, a small study found an average of a 2000-point decrease in TPO antibodies after *H. pylori* eradication [154]. Probiotics have multiple lines of evidence showing that they lower inflammation [9,10] and autoimmunity [9,10,155,156]. An elemental diet was equal to oral prednisone in alleviating rheumatoid arthritis symptomatology [157]. More recently, a more invasive GI therapy of fecal microbiota transplant was found to reduce lupus antibody titers and improve disease activity [158]. These are just a few of the many studies showing an improvement in autoimmunity disease process and symptoms with a GI care model.

In summary, optimizing GI health should be a main therapeutic target for those suffering from thyroid autoimmunity and autoimmunity more generally (Figure 3).

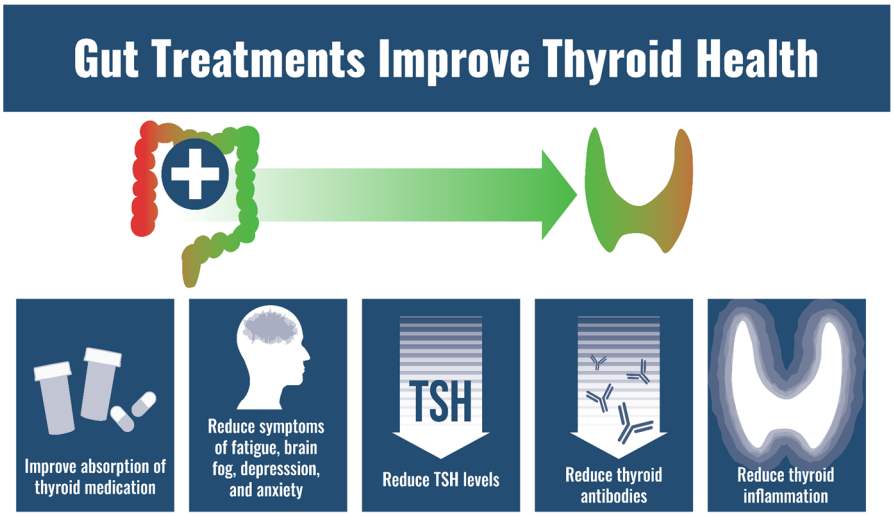

Figure 3. GI effects of GI care on thyroid health.

11. Conclusions

This review has focused on the following points:

- GI conditions can lower thyroid-specific nutrients.
- GI care can improve status of thyroid-specific nutrients.
- GI conditions are much more common than hypothyroidism.
- GI care can resolve symptoms thought to be from "thyroid dysfunction".
- GI health can affect thyroid autoimmunity.

Specific nutrients are certainly imperative for proper thyroid health, but a sole focus on medication or nutrient intake as a way to improve thyroid function may miss a key therapeutic benefit of treating the patient's GI health. Improving gastrointestinal health may indirectly improve thyroid-specific nutrient status and directly improve thyroid function,

reduce autoimmunity, and symptoms thought to be from hypothyroidism (i.e., fatigue, brain fog). Given the prevalence of functional gastrointestinal disorders, it is likely that many hypothyroid patients are still floundering with chronic symptoms because they have yet to identify and treat the root cause of their symptoms; that is their GI health.

The focus on gastrointestinal health in this review is not meant to be myopic. There are numerous environmental and genetic factors that also contribute to the etiology of thyroid disease that go beyond GI health (i.e., chronic stress, environmental toxicants, medications, and autoimmunity). Furthermore, more research is needed in this area of focus because normal thyroid function tests in serum may not necessarily indicate a euthyroid state in all peripheral tissues. For example, there is growing interest in the role of genetic polymorphisms in the deiodinase genes that would affect thyroid hormone concentrations in both blood and tissues [159]. Those with frank hypothyroidism, and some with subclinical hypothyroidism, will need lifelong thyroid medication. However, we contend that GI care cannot be overlooked and should be addressed alongside these other mediators of thyroid dysfunction.

Clinicians may experience superior patient outcomes by understanding and implementing care that addresses the nutrient–GI–thyroid axis and researchers should consider evaluating the associations between these important domains in prospective studies.

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References

1. Saravanan, P.; Chau, W.F.; Roberts, N.; Vedhara, K.; Greenwood, R.; Dayan, C.M. Psychological well-being in patients on "adequate" doses of l-thyroxine: Results of a large, controlled community-based questionnaire study. *Clin. Endocrinol.* **2002**, *57*, 577–585. [CrossRef] [PubMed]
2. Jonklaas, J. Persistent hypothyroid symptoms in a patient with a normal thyroid stimulating hormone level. *Curr. Opin. Endocrinol. Diabetes Obes.* **2017**, *24*, 356–363. [CrossRef] [PubMed]
3. Peterson, S.J.; Cappola, A.R.; Castro, M.R.; Dayan, C.M.; Farwell, A.P.; Hennessey, J.V.; Kopp, P.A.; Ross, D.S.; Samuels, M.H.; Sawka, A.M.; et al. An online survey of hypothyroid patients demonstrates prominent dissatisfaction. *Thyroid* **2018**, *28*, 707–721. [CrossRef]
4. Wouters, H.J.C.M.; Slagter, S.N.; Muller Kobold, A.C.; van der Klauw, M.M.; Wolffenbuttel, B.H.R. Epidemiology of thyroid disorders in the Lifelines Cohort Study (The Netherlands). *PLoS ONE* **2020**, *15*, e0242795. [CrossRef] [PubMed]
5. Tariq, A.; Wert, Y.; Cheriyath, P.; Joshi, R. Effects of Long-Term Combination LT4 and LT3 Therapy for Improving Hypothyroidism and Overall Quality of Life. *South Med. J.* **2018**, *111*, 363–369. [CrossRef]
6. Brechmann, T.; Sperlbaum, A.; Schmiegel, W. Levothyroxine therapy and impaired clearance are the strongest contributors to small intestinal bacterial overgrowth: Results of a retrospective cohort study. *World J. Gastroenterol.* **2017**, *23*, 842–852. [CrossRef] [PubMed]
7. Konrad, P.; Chojnacki, J.; Kaczka, A.; Pawłowicz, M.; Rudnicki, C.; Chojnacki, C. Thyroid dysfunction in patients with small intestinal bacterial overgrowth. *Pol. Merkur. Lek.* **2018**, *44*, 15–18.
8. Talebi, S.; Karimifar, M.; Heidari, Z.; Mohammadi, H.; Askari, G. The effects of synbiotic supplementation on thyroid function and inflammation in hypothyroid patients: A randomized, double-blind, placebo-controlled trial. *Complementary Ther. Med.* **2020**, *48*, 102234. [CrossRef]
9. Lowe, J.R.; Briggs, A.M.; Whittle, S.; Stephenson, M.D. A systematic review of the effects of probiotic administration in inflammatory arthritis. *Complement Ther. Clin. Pract.* **2020**, *40*, 101207. [CrossRef]
10. Mohammed, A.T.; Khattab, M.; Ahmed, A.M.; Turk, T.; Sakr, N.; MKhalil, A.; Abdelhalim, M.; Sawaf, B.; Hirayama, K.; Huy, N.T. The therapeutic effect of probiotics on rheumatoid arthritis: A systematic review and meta-analysis of randomized control trials. *Clin. Rheumatol.* **2017**, *36*, 2697–2707. [CrossRef]

11. García-Collinot, G.; Madrigal-Santillán, E.O.; Martínez-Bencomo, M.A.; Carranza-Muleiro, R.A.; Jara, L.J.; Vera-Lastra, O.; Cruz-Domínguez, M.P. Effectiveness of Saccharomyces boulardii and Metronidazole for Small Intestinal Bacterial Overgrowth in Systemic Sclerosis. *Dig. Dis. Sci.* **2020**, *65*, 1134–1143. [CrossRef]
12. Leventogiannis, K.; Gkolfakis, P.; Spithakis, G.; Tsatali, A.; Pistiki, A.; Sioulas, A.; Triantafyllou, K. Effect of a Preparation of Four Probiotics on Symptoms of Patients with Irritable Bowel Syndrome: Association with Intestinal Bacterial Overgrowth. *Probiotics Antimicrob. Proteins* **2019**, *11*, 627–634. [CrossRef]
13. Küçükemre Aydın, B.; Yıldız, M.; Akgün, A.; Topal, N.; Adal, E.; Önal, H. Children with Hashimoto's Thyroiditis Have Increased Intestinal Permeability: Results of a Pilot Study. *J. Clin. Res. Pediatr. Endocrinol.* **2020**, *12*, 303–307. [CrossRef] [PubMed]
14. Sturgeon, C.; Fasano, A. Zonulin, a regulator of epithelial and endothelial barrier functions, and its involvement in chronic inflammatory diseases. *Tissue Barriers* **2016**, *4*, e1251384. [CrossRef]
15. Fasano, A. Zonulin, regulation of tight junctions, and autoimmune diseases. *Ann. N. Y. Acad. Sci.* **2012**, *1258*, 25–33. [CrossRef]
16. Bjarnason, I.; So, A.; Levi, A.J.; Peters, T.; Williams, P.; Zanelli, G.; Ansell, B. Intestinal permeability and inflammation in rheumatoid arthritis: Effects of non-steroidal anti-inflammatory drugs. *Lancet* **1984**, *2*, 1171–1174. [CrossRef]
17. Goebel, A.; Buhner, S.; Schedel, R.; Lochs, H.; Sprotte, G. Altered intestinal permeability in patients with primary fibromyalgia and in patients with complex regional pain syndrome. *Rheumatology* **2008**, *47*, 1223–1227. [CrossRef]
18. Zheng, D.; Liao, H.; Chen, S.; Liu, X.; Mao, C.; Zhang, C.; Chen, Y. Elevated levels of circulating biomarkers related to leaky gut syndrome and bacterial translocation are associated with graves' disease. *Front. Endocrinol.* **2021**, *12*, 796212. [CrossRef]
19. Youssefi, M.; Tafaghodi, M.; Farsiani, H.; Ghazvini, K.; Keikha, M. Helicobacter pylori infection and autoimmune diseases; Is there an association with systemic lupus erythematosus, rheumatoid arthritis, autoimmune atrophy gastritis and autoimmune pancreatitis? A systematic review and meta-analysis study. *J. Microbiol. Immunol. Infect.* **2021**, *54*, 359–369. [CrossRef]
20. Boutzios, G.; Koukoulioti, E.; Goules, A.V.; Kalliakmanis, I.; Giovannopoulos, I.; Vlachoyiannopoulos, P.; Tzioufas, A.G. Hashimoto Thyroiditis, Anti-Parietal Cell Antibodies: Associations With Autoimmune Diseases and Malignancies. *Front. Endocrinol.* **2022**, *13*, 860880. [CrossRef]
21. Jabbar, A.; Yawar, A.; Waseem, S.; Islam, N.; Ul Haque, N.; Zuberi, L.; Akhter, J. Vitamin B12 deficiency common in primary hypothyroidism. *J. Pak. Med. Assoc.* **2008**, *58*, 258–261. [PubMed]
22. Foley, T.P. The relationship between autoimmune thyroid disease and iodine intake: A review. *Endokrynol. Pol.* **1992**, *43* (Suppl. S1), 53–69. [PubMed]
23. Zhang, Y.; Sun, Y.; He, Z.; Xu, S.; Liu, C.; Li, Y.; Teng, W. Age-specific thyrotropin references decrease over-diagnosis of hypothyroidism in elderly patients in iodine-excessive areas. *Clin. Endocrinol.* **2021**. [CrossRef] [PubMed]
24. Katagiri, R.; Yuan, X.; Kobayashi, S.; Sasaki, S. Effect of excess iodine intake on thyroid diseases in different populations: A systematic review and meta-analyses including observational studies. *PLoS ONE* **2017**, *12*, e0173722. [CrossRef]
25. Chen, Y.; Xiang, Q.; Wang, N.; Zhang, W.; Zhu, C.; Wang, Y.; Lu, Y. Are ethnic differences, urinary iodine status, lead and cadmium exposure associated with thyroid autoimmunity and hypothyroid status? A cross-sectional study. *BMJ Open* **2022**, *12*, e056909. [CrossRef] [PubMed]
26. Yoon, S.J.; Choi, S.R.; Kim, D.M.; Kim, J.U.; Kim, K.W.; Ahn, C.W.; Huh, K.B. The effect of iodine restriction on thyroid function in patients with hypothyroidism due to Hashimoto's thyroiditis. *Yonsei Med. J.* **2003**, *44*, 227–235. [CrossRef] [PubMed]
27. Tajiri, J.; Higashi, K.; Morita, M.; Umeda, T.; Sato, T. Studies of hypothyroidism in patients with high iodine intake. *J. Clin. Endocrinol. Metab.* **1986**, *63*, 412–417. [CrossRef]
28. Manousou, S.; Stål, M.; Larsson, C.; Mellberg, C.; Lindahl, B.; Eggertsen, R.; Nyström, H.F. A Paleolithic-type diet results in iodine deficiency: A 2-year randomized trial in postmenopausal obese women. *Eur. J. Clin. Nutr.* **2018**, *72*, 124–129. [CrossRef]
29. Eveleigh, E.R.; Coneyworth, L.J.; Avery, A.; Welham, S.J.M. Vegans, vegetarians, and omnivores: How does dietary choice influence iodine intake? A systematic review. *Nutrients* **2020**, *12*, 1606. [CrossRef]
30. Wichman, J.; Winther, K.H.; Bonnema, S.J.; Hegedüs, L. Selenium Supplementation Significantly Reduces Thyroid Autoantibody Levels in Patients with Chronic Autoimmune Thyroiditis: A Systematic Review and Meta-Analysis. *Thyroid* **2016**, *26*, 1681–1692. [CrossRef] [PubMed]
31. Sun, C.; Zhu, M.; Li, L.; Fan, H.; Lv, F.; Zhu, D. Clinical Observation of Levothyroxine Sodium Combined with Selenium in the Treatment of Patients with Chronic Lymphocytic Thyroiditis and Hypothyroidism and the Effects on Thyroid Function, Mood, and Inflammatory Factors. *Evid.-Based Complementary Altern. Med.* **2021**, *2021*, 5471281. [CrossRef] [PubMed]
32. Kryczyk-Kozioł, J.; Zagrodzki, P.; Prochownik, E.; Błażewska-Gruszczyk, A.; Słowiaczek, M.; Sun, Q.; Bartyzel, M. Positive effects of selenium supplementation in women with newly diagnosed Hashimoto's thyroiditis in an area with low selenium status. *Int. J. Clin. Pract.* **2021**, *75*, e14484. [CrossRef]
33. Qiu, Y.; Xing, Z.; Xiang, Q.; Yang, Q.; Zhu, J.; Su, A. Insufficient evidence to support the clinical efficacy of selenium supplementation for patients with chronic autoimmune thyroiditis. *Endocrine* **2021**, *73*, 384–397. [CrossRef] [PubMed]
34. Winther, K.H.; Bonnema, S.J.; Hegedüs, L. Is selenium supplementation in autoimmune thyroid diseases justified? *Curr. Opin. Endocrinol. Diabetes Obes.* **2017**, *24*, 348–355. [CrossRef]
35. Duntas, L.H. The evolving role of selenium in the treatment of graves' disease and ophthalmopathy. *J. Thyroid Res.* **2012**, *2012*, 736161. [CrossRef]
36. Wertenbruch, T.; Willenberg, H.S.; Sagert, C.; Nguyen TB, T.; Bahlo, M.; Feldkamp, J.; Schott, M. Serum selenium levels in patients with remission and relapse of graves' disease. *Med. Chem.* **2007**, *3*, 281–284. [CrossRef]

37. Filipowicz, D.; Majewska, K.; Kalantarova, A.; Szczepanek-Parulska, E.; Ruchała, M. The rationale for selenium supplementation in patients with autoimmune thyroiditis, according to the current state of knowledge. *Endokrynol. Pol.* **2021**, *72*, 153–162. [CrossRef] [PubMed]
38. Pirola, I.; Rotondi, M.; Cristiano, A.; Maffezzoni, F.; Pasquali, D.; Marini, F.; Cappelli, C. Selenium supplementation in patients with subclinical hypothyroidism affected by autoimmune thyroiditis: Results of the SETI study. *Endocrinol. Diabetes Nutr.* **2020**, *67*, 28–35. [CrossRef]
39. Pace, C.; Tumino, D.; Russo, M.; Le Moli, R.; Naselli, A.; Borzì, G.; Frasca, F. Role of selenium and myo-inositol supplementation on autoimmune thyroiditis progression. *Endocr. J.* **2020**, *67*, 1093–1098. [CrossRef]
40. Nordio, M.; Basciani, S. Myo-inositol plus selenium supplementation restores euthyroid state in Hashimoto's patients with subclinical hypothyroidism. *Eur. Rev. Med. Pharmacol. Sci.* **2017**, *21* (Suppl. S2), 51–59.
41. Nordio, M.; Pajalich, R. Combined treatment with Myo-inositol and selenium ensures euthyroidism in subclinical hypothyroidism patients with autoimmune thyroiditis. *J. Thyroid Res.* **2013**, *2013*, 424163. [CrossRef]
42. Appunni, S.; Rubens, M.; Ramamoorthy, V.; Saxena, A.; Tonse, R.; Veledar, E.; McGranaghan, P. Association between vitamin D deficiency and hypothyroidism: Results from the National Health and Nutrition Examination Survey (NHANES) 2007–2012. *BMC Endocr. Disord.* **2021**, *21*, 224. [CrossRef] [PubMed]
43. Bozkurt, N.C.; Karbek, B.; Ucan, B.; Sahin, M.; Cakal, E.; Ozbek, M.; Delibasi, T. The association between severity of vitamin D deficiency and Hashimoto's thyroiditis. *Endocr. Pract.* **2013**, *19*, 479–484. [CrossRef] [PubMed]
44. Zhang, J.; Chen, Y.; Li, H.; Li, H. Effects of vitamin D on thyroid autoimmunity markers in Hashimoto's thyroiditis: Systematic review and meta-analysis. *J. Int. Med. Res.* **2021**, *49*, 3000605211060675. [CrossRef] [PubMed]
45. Iron Deficiency May Explain Persistent Hypothyroidism Symptoms | MDedge Endocrinology. Available online: https://www.mdedge.com/endocrinology/article/104350/pituitary-thyroid-adrenal-disorders/iron-deficiency-may-explain (accessed on 1 July 2021).
46. Rayman, M.P. Multiple nutritional factors and thyroid disease, with particular reference to autoimmune thyroid disease. *Proc. Nutr. Soc.* **2019**, *78*, 34–44. [CrossRef] [PubMed]
47. Luo, J.; Wang, X.; Yuan, L.; Guo, L. Iron Deficiency, a Risk Factor of Thyroid Disorders in Reproductive-Age and Pregnant Women: A Systematic Review and Meta-Analysis. *Front. Endocrinol.* **2021**, *12*, 629831. [CrossRef]
48. Aktaş, H.Ş. Vitamin B12 and Vitamin D Levels in Patients with Autoimmune Hypothyroidism and Their Correlation with Anti-Thyroid Peroxidase Antibodies. *Med. Princ. Pract.* **2020**, *29*, 364–370. [CrossRef] [PubMed]
49. Kacharava, T.; Giorgadze, E.; Janjgava, S.; Lomtadze, N.; Iamze, T. Correlation between Vitamin B12 Deficiency and Autoimmune Thyroid Diseases. *Endocr. Metab. Immune Disord. Drug Targets* **2022**. [CrossRef]
50. Talebi, S.; Ghaedi, E.; Sadeghi, E.; Mohammadi, H.; Hadi, A.; Clark, C.C.; Askari, G. Trace Element Status and Hypothyroidism: A Systematic Review and Meta-analysis. *Biol. Trace Elem. Res.* **2020**, *197*, 1–14. [CrossRef]
51. Ertek, S.; Cicero, A.F.; Caglar, O.; Erdogan, G. Relationship between serum zinc levels, thyroid hormones and thyroid volume following successful iodine supplementation. *Hormones* **2010**, *9*, 263–268. [CrossRef]
52. Szczepanik, J.; Podgórski, T.; Domaszewska, K. The Level of Zinc, Copper and Antioxidant Status in the Blood Serum of Women with Hashimoto's Thyroiditis. *Int. J. Environ. Res. Public Health* **2021**, *18*, 7805. [CrossRef] [PubMed]
53. Mazidi, M.; Rezaie, P.; Banach, M. Effect of magnesium supplements on serum C-reactive protein: A systematic review and meta-analysis. *Arch. Med. Sci.* **2018**, *14*, 707–716. [CrossRef] [PubMed]
54. Wang, K.; Wei, H.; Zhang, W.; Li, Z.; Ding, L.; Yu, T.; Zhu, M. Severely low serum magnesium is associated with increased risks of positive anti-thyroglobulin antibody and hypothyroidism: A cross-sectional study. *Sci. Rep.* **2018**, *8*, 9904. [CrossRef] [PubMed]
55. Cox, I.M.; Campbell, M.J.; Dowson, D. Red blood cell magnesium and chronic fatigue syndrome. *Lancet* **1991**, *337*, 757–760. [CrossRef]
56. Rao, S.S.C.; Brenner, D.M. Efficacy and Safety of Over-the-Counter Therapies for Chronic Constipation: An Updated Systematic Review. *Am. J. Gastroenterol.* **2021**, *116*, 1156–1181. [CrossRef] [PubMed]
57. Kennedy, D.O.; Veasey, R.C.; Watson, A.W.; Dodd, F.L.; Jones, E.K.; Tiplady, B.; Haskell, C.F. Vitamins and psychological functioning: A mobile phone assessment of the effects of a B vitamin complex, vitamin C and minerals on cognitive performance and subjective mood and energy. *Hum. Psychopharmacol.* **2011**, *26*, 338–347. [CrossRef]
58. Moncayo, R.; Moncayo, H. Proof of concept of the WOMED model of benign thyroid disease: Restitution of thyroid morphology after correction of physical and psychological stressors and magnesium supplementation. *BBA Clin.* **2015**, *3*, 113–122. [CrossRef]
59. Carabotti, M.; Lahner, E.; Esposito, G.; Sacchi, M.C.; Severi, C.; Annibale, B. Upper gastrointestinal symptoms in autoimmune gastritis: A cross-sectional study. *Medicine* **2017**, *96*, e5784. [CrossRef]
60. Sipponen, P.; Maaroos, H.-I. Chronic gastritis. *Scand. J. Gastroenterol.* **2015**, *50*, 657–667. [CrossRef]
61. Khayyat, Y.; Attar, S. Vitamin D Deficiency in Patients with Irritable Bowel Syndrome: Does it Exist? *Oman Med. J.* **2015**, *30*, 115–118. [CrossRef]
62. Nwosu, B.U.; Maranda, L.; Candela, N. Vitamin D status in pediatric irritable bowel syndrome. *PLoS ONE* **2017**, *12*, e0172183. [CrossRef]
63. Losurdo, G.; Salvatore D'Abramo, F.; Indellicati, G.; Lillo, C.; Ierardi, E.; Di Leo, A. The Influence of Small Intestinal Bacterial Overgrowth in Digestive and Extra-Intestinal Disorders. *Int. J. Mol. Sci.* **2020**, *21*, 3531. [CrossRef] [PubMed]

64. Rezazadegan, M.; Soheilipour, M.; Tarrahi, M.J.; Amani, R. Correlation Between Zinc Nutritional Status with Serum Zonulin and Gastrointestinal Symptoms in Diarrhea-Predominant Irritable Bowel Syndrome: A Case-Control Study. *Dig. Dis. Sci.* **2022**, *67*, 3632–3638. [CrossRef] [PubMed]
65. Melchior, C.; Algera, J.; Colomier, E.; Törnblom, H.; Simrén, M.; Störsrud, S. Food avoidance and restriction in irritable bowel syndrome: Relevance for symptoms, quality of life and nutrient intake. *Clin. Gastroenterol. Hepatol.* **2022**, *20*, 1290–1298.e4. [CrossRef]
66. Forbes, A.; Escher, J.; Hébuterne, X.; Kłęk, S.; Krznaric, Z.; Schneider, S.; Bischoff, S.C. ESPEN guideline: Clinical nutrition in inflammatory bowel disease. *Clin. Nutr.* **2017**, *36*, 321–347. [CrossRef] [PubMed]
67. Lambert, K.; Pappas, D.; Miglioretto, C.; Javadpour, A.; Reveley, H.; Frank, L.; Grimm, M.C.; Samocha-Bonet, D.; Hold, G.L. Systematic review with meta-analysis: Dietary intake in adults with inflammatory bowel disease. *Aliment. Pharmacol. Ther.* **2021**, *54*, 742–754. [CrossRef] [PubMed]
68. Ishihara, J.; Arai, K.; Kudo, T.; Nambu, R.; Tajiri, H.; Aomatsu, T.; Mizuochi, T. Serum Zinc and Selenium in Children with Inflammatory Bowel Disease: A Multicenter Study in Japan. *Dig. Dis. Sci.* **2022**, *67*, 2485–2491. [CrossRef]
69. Delvecchio, M.; Bizzoco, F.; Lapolla, R.; Gentile, A.; Carrozza, C.; Barone, M.; Francavilla, R. Iodine absorption in celiac children: A longitudinal pilot study. *Nutrients* **2021**, *13*, 808. [CrossRef]
70. Hutchinson, C.; Geissler, C.A.; Powell, J.J.; Bomford, A. Proton pump inhibitors suppress absorption of dietary non-haem iron in hereditary haemochromatosis. *Gut* **2007**, *56*, 1291–1295. [CrossRef]
71. Ozutemiz, A.O.; Aydin, H.H.; Isler, M.; Celik, H.A.; Batur, Y. Effect of omeprazole on plasma zinc levels after oral zinc administration. *Indian J. Gastroenterol.* **2002**, *21*, 216–218.
72. Allen, L.H. Vitamin B-12. *Adv. Nutr.* **2012**, *3*, 54–55. [CrossRef]
73. Jalal, M.; Campbell, J.A.; Tesfaye, S.; Al-Mukhtar, A.; Hopper, A.D. Yield of testing for micronutrient deficiencies associated with pancreatic exocrine insufficiency in a clinical setting: An observational study. *World J. Clin. Cases* **2021**, *9*, 11320–11329. [CrossRef]
74. Phillips, M.E.; Hopper, A.D.; Leeds, J.S.; Roberts, K.J.; McGeeney, L.; Duggan, S.N.; Kumar, R. Consensus for the management of pancreatic exocrine insufficiency: UK practical guidelines. *BMJ Open Gastroenterol.* **2021**, *8*, e000643. [CrossRef]
75. Barkhidarian, B.; Roldos, L.; Iskandar, M.M.; Saedisomeolia, A.; Kubow, S. Probiotic supplementation and micronutrient status in healthy subjects: A systematic review of clinical trials. *Nutrients* **2021**, *13*, 3001. [CrossRef]
76. Mohammad, M.A.; Molloy, A.; Scott, J.; Hussein, L. Plasma cobalamin and folate and their metabolic markers methylmalonic acid and total homocysteine among Egyptian children before and after nutritional supplementation with the probiotic bacteria Lactobacillus acidophilus in yoghurt matrix. *Int. J. Food Sci. Nutr.* **2006**, *57*, 470–480. [CrossRef]
77. Sandroni, A.; House, E.; Howard, L.; DellaValle, D.M. Synbiotic Supplementation Improves Response to Iron Supplementation in Female Athletes during Training. *J. Diet Suppl.* **2022**, *19*, 366–380. [CrossRef]
78. Tremblay, A.; Xu, X.; Colee, J.; Tompkins, T.A. Efficacy of a Multi-Strain Probiotic Formulation in Pediatric Populations: A Comprehensive Review of Clinical Studies. *Nutrients* **2021**, *13*, 1908. [CrossRef]
79. Axling, U.; Önning, G.; Martinsson Niskanen, T.; Larsson, N.; Hansson, S.R.; Hulthén, L. The effect of Lactiplantibacillus plantarum 299v together with a low dose of iron on iron status in healthy pregnant women: A randomized clinical trial. *Acta Obstet. Gynecol. Scand.* **2021**, *100*, 1602–1610. [CrossRef]
80. Wang, F.; Feng, J.; Chen, P.; Liu, X.; Ma, M.; Zhou, R.; Zhao, Q. Probiotics in Helicobacter pylori eradication therapy: Systematic review and network meta-analysis. *Clin. Res. Hepatol. Gastroenterol.* **2017**, *41*, 466–475. [CrossRef]
81. Penumetcha, S.S.; Ahluwalia, S.; Irfan, R.; Khan, S.A.; Reddy, S.R.; Lopez ME, V.; Mohammed, L. The efficacy of probiotics in the management of helicobacter pylori: A systematic review. *Cureus* **2021**, *13*, e20483. [CrossRef]
82. Ferreiro, B.; Llopis-Salinero, S.; Lardies, B.; Granados-Colomina, C.; Milà-Villarroel, R. Clinical and Nutritional Impact of a Semi-Elemental Hydrolyzed Whey Protein Diet in Patients with Active Crohn's Disease: A Prospective Observational Study. *Nutrients* **2021**, *13*, 3623. [CrossRef] [PubMed]
83. Teahon, K.; Pearson, M.; Smith, T.; Bjarnason, I. Alterations in nutritional status and disease activity during treatment of Crohn's disease with elemental diet. *Scand. J. Gastroenterol.* **1995**, *30*, 54–60. [CrossRef]
84. Wilson, D.; Evans, M.; Weaver, E.; Shaw, A.L.; Klein, G.L. Evaluation of serum-derived bovine immunoglobulin protein isolate in subjects with diarrhea-predominant irritable bowel syndrome. *Clin. Med. Insights Gastroenterol.* **2013**, *6*, 49–60. [CrossRef]
85. Petschow, B.W.; Burnett, B.; Shaw, A.L.; Weaver, E.M.; Klein, G.L. Serum-derived bovine immunoglobulin/protein isolate: Postulated mechanism of action for management of enteropathy. *Clin. Exp. Gastroenterol.* **2014**, *7*, 181–190. [CrossRef]
86. Ruscio, M.; Guard, G.; Mather, J. Symptoms Originally Attributed to Thyroid Dysfunction Were Instead Caused by Suboptimal Gastrointestinal Health: A Case Series and Literature Review. *Integr. Med. Clin. J.* **2022**, *21*, 22–29.
87. Carlé, A.; Pedersen, I.B.; Knudsen, N.; Perrild, H.; Ovesen, L.; Laurberg, P. Hypothyroid symptoms and the likelihood of overt thyroid failure: A population-based case-control study. *Eur. J. Endocrinol.* **2014**, *171*, 593–602. [CrossRef]
88. Siegmann, E.-M.; Müller, H.H.O.; Luecke, C.; Philipsen, A.; Kornhuber, J.; Grömer, T.W. Association of Depression and Anxiety Disorders With Autoimmune Thyroiditis: A Systematic Review and Meta-analysis. *JAMA Psychiatry* **2018**, *75*, 577–584. [CrossRef]
89. Böhn, L.; Störsrud, S.; Törnblom, H.; Bengtsson, U.; Simrén, M. Self-reported food-related gastrointestinal symptoms in IBS are common and associated with more severe symptoms and reduced quality of life. *Am. J. Gastroenterol.* **2013**, *108*, 634–641. [CrossRef] [PubMed]

90. Piche, T.; Huet, P.M.; Gelsi, E.; Barjoan, E.M.; Cherick, F.; Caroli-Bosc, F.X.; Tran, A. Fatigue in irritable bowel syndrome: Characterization and putative role of leptin. *Eur. J. Gastroenterol. Hepatol.* **2007**, *19*, 237–243. [CrossRef] [PubMed]
91. Schwille-Kiuntke, J.; Ittermann, T.; Schmidt, C.O.; Grabe, H.J.; Lerch, M.M.; Völzke, H.; Schauer, B. Quality of life and sleep in individuals with irritable bowel syndrome according to different diagnostic criteria and inflammatory bowel diseases: A comparison using data from a population-based survey. *Z. Für Gastroenterol.* **2022**, *60*, 299–309. [CrossRef] [PubMed]
92. Mohammed, A.A.; Moustafa, H.A.; Nour-Eldein, H.; Saudi, R.A. Association of anxiety-depressive disorders with irritable bowel syndrome among patients attending a rural family practice center: A comparative cross-sectional study. *Gen. Psych.* **2021**, *34*, e100553. [CrossRef] [PubMed]
93. Kovács, Z.; Kovács, F. Depressive and anxiety symptoms, coping strategies in patients with irritable bowel syndrome and inflammatory bowel disease. *Psychiatr. Hung.* **2007**, *22*, 212–221. [PubMed]
94. Jerndal, P.; Ringström, G.; Agerforz, P.; Karpefors, M.; Akkermans, L.M.; Bayati, A.; Simrén, M. Gastrointestinal-specific anxiety: An important factor for severity of GI symptoms and quality of life in IBS. *Neurogastroenterol. Motil.* **2010**, *22*, 646-e179. [CrossRef] [PubMed]
95. Svedlund, J.; Sjödin, I.; Dotevall, G.; Gillberg, R. Upper gastrointestinal and mental symptoms in the irritable bowel syndrome. *Scand. J. Gastroenterol.* **1985**, *20*, 595–601. [CrossRef] [PubMed]
96. Wang, B.; Duan, R.; Duan, L. Prevalence of sleep disorder in irritable bowel syndrome: A systematic review with meta-analysis. *Saudi. J. Gastroenterol.* **2018**, *24*, 141–150. [CrossRef]
97. Grover, M.; Kanazawa, M.; Palsson, O.S.; Chitkara, D.K.; Gangarosa, L.M.; Drossman, D.A.; Whitehead, W.E. Small intestinal bacterial overgrowth in irritable bowel syndrome: Association with colon motility, bowel symptoms, and psychological distress. *Neurogastroenterol. Motil.* **2008**, *20*, 998–1008. [CrossRef] [PubMed]
98. Van Gils, T.; Nijeboer, P.; IJssennagger, C.E.; Sanders, D.S.; Mulder, C.J.; Bouma, G. Prevalence And Characterization Of Self-Reported Gluten Sensitivity In The Netherlands. *Nutrients* **2016**, *8*, 714. [CrossRef]
99. Volta, U.; Bardella, M.T.; Calabrò, A.; Troncone, R.; Corazza, G.R.; Study Group for Non-Celiac Gluten Sensitivity. An Italian prospective multicenter survey on patients suspected of having non-celiac gluten sensitivity. *BMC Med.* **2014**, *12*, 85. [CrossRef]
100. Losurdo, G.; Principi, M.; Iannone, A.; Amoruso, A.; Ierardi, E.; Di Leo, A.; Barone, M. Extra-intestinal manifestations of non-celiac gluten sensitivity: An expanding paradigm. *World J. Gastroenterol.* **2018**, *24*, 1521–1530. [CrossRef] [PubMed]
101. Peters, S.L.; Biesiekierski, J.R.; Yelland, G.W.; Muir, J.G.; Gibson, P.R. Randomised clinical trial: Gluten may cause depression in subjects with non-coeliac gluten sensitivity—An exploratory clinical study. *Aliment. Pharmacol. Ther.* **2014**, *39*, 1104–1112. [CrossRef]
102. Vergnat, M.; Suzanne, J.; Entraygues, H.; Laurent, R.; Gisselbrecht, H.; Agache, P. Cutaneous manifestations of malabsorption diseases (author's transl). *Ann. Dermatol. Venereol.* **1978**, *105*, 1009–1016. [PubMed]
103. O'Neill, C.A.; Monteleone, G.; McLaughlin, J.T.; Paus, R. The gut-skin axis in health and disease: A paradigm with therapeutic implications. *Bioessays* **2016**, *38*, 1167–1176. [CrossRef] [PubMed]
104. Prospero, L.; Riezzo, G.; Linsalata, M.; Orlando, A.; D'Attoma, B.; Russo, F. Psychological and Gastrointestinal Symptoms of Patients with Irritable Bowel Syndrome Undergoing a Low-FODMAP Diet: The Role of the Intestinal Barrier. *Nutrients* **2021**, *13*, 2469. [CrossRef] [PubMed]
105. Yang, B.; Wei, J.; Ju, P.; Chen, J. Effects of regulating intestinal microbiota on anxiety symptoms: A systematic review. *Gen Psych.* **2019**, *32*, e100056. [CrossRef] [PubMed]
106. Marum, A.P.; Moreira, C.; Saraiva, F.; Tomas-Carus, P.; Sousa-Guerreiro, C. A low fermentable oligo-di-mono saccharides and polyols (FODMAP) diet reduced pain and improved daily life in fibromyalgia patients. *Scand. J. Pain.* **2016**, *13*, 166–172. [CrossRef] [PubMed]
107. Rao, A.V.; Bested, A.C.; Beaulne, T.M.; Katzman, M.A.; Iorio, C.; Berardi, J.M.; Logan, A.C. A randomized, double-blind, placebo-controlled pilot study of a probiotic in emotional symptoms of chronic fatigue syndrome. *Gut Pathog.* **2009**, *1*, 6. [CrossRef]
108. Ng, Q.X.; Peters, C.; Ho, C.Y.X.; Lim, D.Y.; Yeo, W.-S. A meta-analysis of the use of probiotics to alleviate depressive symptoms. *J. Affect. Disord.* **2018**, *228*, 13–19. [CrossRef] [PubMed]
109. Goh, K.K.; Liu, Y.-W.; Kuo, P.-H.; Chung, Y.-C.E.; Lu, M.-L.; Chen, C.-H. Effect of probiotics on depressive symptoms: A meta-analysis of human studies. *Psychiatry Res.* **2019**, *282*, 112568. [CrossRef]
110. Huang, R.; Wang, K.; Hu, J. Effect of Probiotics on Depression: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Nutrients* **2016**, *8*, 483. [CrossRef] [PubMed]
111. Liu, R.T.; Walsh, R.F.L.; Sheehan, A.E. Prebiotics and probiotics for depression and anxiety: A systematic review and meta-analysis of controlled clinical trials. *Neurosci. Biobehav. Rev.* **2019**, *102*, 13–23. [CrossRef] [PubMed]
112. Lew, L.C.; Hor, Y.Y.; Yusoff NA, A.; Choi, S.B.; Yusoff, M.S.; Roslan, N.S.; Liong, M.T. Probiotic Lactobacillus plantarum P8 alleviated stress and anxiety while enhancing memory and cognition in stressed adults: A randomised, double-blind, placebo-controlled study. *Clin. Nutr.* **2019**, *38*, 2053–2064. [CrossRef]
113. Allen, A.P.; Hutch, W.; Borre, Y.E.; Kennedy, P.J.; Temko, A.; Boylan, G.; Clarke, G. Bifidobacterium longum 1714 as a translational psychobiotic: Modulation of stress, electrophysiology and neurocognition in healthy volunteers. *Transl. Psychiatry* **2016**, *6*, e939. [CrossRef] [PubMed]

114. Hwang, Y.H.; Park, S.; Paik, J.W.; Chae, S.W.; Kim, D.H.; Jeong, D.G.; Chung, Y.C. Efficacy and Safety of *Lactobacillus Plantarum* C29-Fermented Soybean (DW2009) in Individuals with Mild Cognitive Impairment: A 12-Week, Multi-Center, Randomized, Double-Blind, Placebo-Controlled Clinical Trial. *Nutrients* **2019**, *11*, 305. [CrossRef] [PubMed]
115. Wei, F.; Zhou, L.; Wang, Q.; Zheng, G.; Su, S. Effect of Compound Lactic Acid Bacteria Capsules on the Small Intestinal Bacterial Overgrowth in Patients with Depression and Diabetes: A Blinded Randomized Controlled Clinical Trial. *Dis. Markers* **2022**, *2022*, 6721695. [CrossRef] [PubMed]
116. De Rooij, W.E.; Vlieg–Boerstra, B.; Warners, M.J.; Van Ampting, M.T.; van Esch, B.C.; Eussen, S.R.; Bredenoord, A.J. Effect of amino acid-based formula added to four-food elimination in adult eosinophilic esophagitis patients: A randomized clinical trial. *Neurogastroenterol. Motil.* **2022**, *34*, e14291. [CrossRef]
117. McMurdy, J.M. High calorie elemental diet improves outcomes and quality of life for tube FED adolescents. *J. Am. Diet Assoc.* **1999**, *99*, A128. [CrossRef]
118. Flamm, S.L.; Mullen, K.D.; Heimanson, Z.; Sanyal, A.J. Rifaximin has the potential to prevent complications of cirrhosis. *Ther. Adv. Gastroenterol.* **2018**, *11*, 1756284818800307. [CrossRef] [PubMed]
119. Flamm, S.L. Rifaximin treatment for reduction of risk of overt hepatic encephalopathy recurrence. *Ther. Adv. Gastroenterol.* **2011**, *4*, 199–206. [CrossRef]
120. Caraceni, P.; Vargas, V.; Solà, E.; Alessandria, C.; de Wit, K.; Trebicka, J.; Watson, H. The use of rifaximin in patients with cirrhosis. *Hepatology* **2021**, *74*, 1660–1673. [CrossRef] [PubMed]
121. Maes, M.; Leunis, J.-C. Normalization of leaky gut in chronic fatigue syndrome (CFS) is accompanied by a clinical improvement: Effects of age, duration of illness and the translocation of LPS from gram-negative bacteria. *Neuroendocrinol. Lett.* **2008**, *29*, 902–910. [PubMed]
122. El-Salhy, M.; Winkel, R.; Casen, C.; Hausken, T.; Gilja, O.H.; Hatlebakk, J.G. Efficacy of fecal microbiota transplantation for patients with irritable bowel syndrome at three years after transplantation. *Gastroenterology* **2022**, *6*, ofz398. [CrossRef]
123. Enko, D.; Meinitzer, A.; Mangge, H.; Kriegshäuser, G.; Halwachs-Baumann, G.; Reininghaus, E.Z.; Schnedl, W.J. Concomitant prevalence of low serum diamine oxidase activity and carbohydrate malabsorption. *Can. J. Gastroenterol. Hepatol.* **2016**, *2016*, 4893501. [CrossRef] [PubMed]
124. Hollowell, J.G.; Staehling, N.W.; Flanders, W.D.; Hannon, W.H.; Gunter, E.W.; Spencer, C.A.; Braverman, L.E. Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). *J. Clin. Endocrinol. Metab.* **2002**, *87*, 489–499. [CrossRef] [PubMed]
125. Aghini-Lombardi, F.; Antonangeli, L.; Martino, E.; Vitti, P.; Maccherini, D.; Leoli, F.; Pinchera, A. The spectrum of thyroid disorders in an iodine-deficient community: The Pescopagano survey. *J. Clin. Endocrinol. Metab.* **1999**, *84*, 561–566. [CrossRef] [PubMed]
126. Jain, R.B. Thyroid Profile of the Reference United States Population: Data from NHANES 2007–2012. *Int. Arch. Endocrinol. Clin. Res.* **2015**, *1*, 1–8. [CrossRef]
127. Garmendia Madariaga, A.; Santos Palacios, S.; Guillén-Grima, F.; Galofré, J.C. The incidence and prevalence of thyroid dysfunction in Europe: A meta-analysis. *J. Clin. Endocrinol. Metab.* **2014**, *99*, 923–931. [CrossRef]
128. Talley, N.J.; Zinsmeister, A.R.; Van Dyke, C.; Melton, L.J. Epidemiology of colonic symptoms and the irritable bowel syndrome. *Gastroenterology* **1991**, *101*, 927–934. [CrossRef]
129. Lovell, R.M.; Ford, A.C. Global prevalence of and risk factors for irritable bowel syndrome: A meta-analysis. *Clin. Gastroenterol. Hepatol.* **2012**, *10*, 712–721.e4. [CrossRef]
130. Thompson, W.G.; Irvine, E.J.; Pare, P.; Ferrazzi, S.; Rance, L. Functional gastrointestinal disorders in Canada: First population-based survey using Rome II criteria with suggestions for improving the questionnaire. *Dig. Dis. Sci.* **2002**, *47*, 225–235. [CrossRef] [PubMed]
131. Canavan, C.; West, J.; Card, T. The epidemiology of irritable bowel syndrome. *Clin. Epidemiol.* **2014**, *6*, 71–80. [CrossRef]
132. Livadas, S.; Bothou, C.; Androulakis, I.; Boniakos, A.; Angelopoulos, N.; Duntas, L. Levothyroxine replacement therapy and overuse: A timely diagnostic approach. *Thyroid* **2018**, *28*, 1580–1586. [CrossRef]
133. Ross, D.S. Treating hypothyroidism is not always easy: When to treat subclinical hypothyroidism, TSH goals in the elderly, and alternatives to levothyroxine monotherapy. *J. Intern. Med.* **2022**, *291*, 128–140. [CrossRef]
134. Abu-Helalah, M.; Alshraideh, H.A.; Al-Sarayreh, S.A.; Al-Hader, A. Transient high thyroid stimulating hormone and hypothyroidism incidence during follow up of subclinical hypothyroidism. *Endocr. Regul.* **2021**, *55*, 204–214. [CrossRef]
135. Meyerovitch, J.; Rotman-Pikielny, P.; Sherf, M.; Battat, E.; Levy, Y.; Surks, M.I. Serum thyrotropin measurements in the community: Five-year follow-up in a large network of primary care physicians. *Arch. Intern. Med.* **2007**, *167*, 1533–1538. [CrossRef]
136. Zhao, C.; Wang, Y.; Xiao, L.; Li, L. Effect of Levothyroxine on Older Patients With Subclinical Hypothyroidism: A Systematic Review and Meta-Analysis. *Front. Endocrinol.* **2022**, *13*, 913749. [CrossRef]
137. Hashimoto, K. Update on subclinical thyroid dysfunction. *Endocr. J.* **2022**, *69*, 725–738. [CrossRef]
138. Lyko, C.; Blum, M.R.; Abolhassani, N.; Stuber, M.J.; Del Giovane, C.; Feller, M.; Rodondi, N. Thyroid antibodies and levothyroxine effects in subclinical hypothyroidism: A pooled analysis of two randomized controlled trials. *J. Intern. Med.* **2022**. [CrossRef]
139. Büchi, A.E.; Feller, M.; Netzer, S.; Blum, M.R.; Rodriguez, E.G.; Collet, T.H.; Aeberli, D. Bone geometry in older adults with subclinical hypothyroidism upon levothyroxine therapy: A nested study within a randomized placebo controlled trial. *Bone* **2022**, *161*, 116404. [CrossRef]

140. Biondi, B.; Cappola, A.R. Subclinical hypothyroidism in older individuals. *Lancet Diabetes Endocrinol.* **2022**, *10*, 129–141. [CrossRef]
141. Burgos, N.; Toloza, F.J.; Singh Ospina, N.M.; Brito, J.P.; Salloum, R.G.; Hassett, L.C.; Maraka, S. Clinical Outcomes After Discontinuation of Thyroid Hormone Replacement: A Systematic Review and Meta-Analysis. *Thyroid* **2021**, *31*, 740–751. [CrossRef]
142. Virili, C.; Brusca, N.; Capriello, S.; Centanni, M. Levothyroxine therapy in gastric malabsorptive disorders. *Front. Endocrinol.* **2020**, *11*, 621616. [CrossRef]
143. Ribichini, D.; Fiorini, G.; Repaci, A.; Castelli, V.; Gatta, L.; Vaira, D.; Pasquali, R. Tablet and oral liquid L-thyroxine formulation in the treatment of naïve hypothyroid patients with Helicobacter pylori infection. *Endocrine* **2017**, *57*, 394–401. [CrossRef] [PubMed]
144. Bugdaci, M.S.; Zuhur, S.S.; Sokmen, M.; Toksoy, B.; Bayraktar, B.; Altuntas, Y. The role of Helicobacter pylori in patients with hypothyroidism in whom could not be achieved normal thyrotropin levels despite treatment with high doses of thyroxine. *Helicobacter* **2011**, *16*, 124–130. [CrossRef] [PubMed]
145. Centanni, M.; Gargano, L.; Canettieri, G.; Viceconti, N.; Franchi, A.; Fave, G.D.; Annibale, B. Thyroxine in goiter, Helicobacter pylori infection, and chronic gastritis. *New Engl. J. Med.* **2006**, *354*, 1787–1795. [CrossRef] [PubMed]
146. Bohinc Henderson, B. Levothyroxine Sodium Oral Solution Normalizes Thyroid Function in a Patient with Hashimoto's Disease, Gastritis, Diabetic Gastroparesis, and Small Intestinal Bacterial Overgrowth (SIBO). *Int. Med. Case Rep. J.* **2021**, *14*, 627–632. [CrossRef] [PubMed]
147. Asik, M.; Gunes, F.; Binnetoglu, E.; Eroglu, M.; Bozkurt, N.; Sen, H.; Ukinc, K. Decrease in TSH levels after lactose restriction in Hashimoto's thyroiditis patients with lactose intolerance. *Endocrine* **2014**, *46*, 279–284. [CrossRef] [PubMed]
148. Virili, C.; Bassotti, G.; Santaguida, M.G.; Iuorio, R.; Del Duca, S.C.; Mercuri, V.; Centanni, M. Atypical celiac disease as cause of increased need for thyroxine: A systematic study. *J. Clin. Endocrinol. Metab.* **2012**, *97*, E419–E422. [CrossRef] [PubMed]
149. Virili, C.; Stramazzo, I.; Centanni, M. Gut microbiome and thyroid autoimmunity. *Best Pract. Res. Clin. Endocrinol. Metab.* **2021**, *35*, 101506. [CrossRef]
150. Zangiabadian, M.; Mirsaeidi, M.; Pooyafar, M.H.; Goudarzi, M.; Nasiri, M.J. Associations of Yersinia Enterocolitica Infection with Autoimmune Thyroid Diseases: A Systematic Review and Meta-Analysis. *Endocr. Metab. Immune Disord.-Drug Targets* **2021**, *21*, 682–687. [CrossRef]
151. Wenzel, B.E.; Heesemann, J.; Wenzel, K.W.; Scriba, P.C. Patients with autoimmune thyroid diseases have antibodies to plasmid encoded proteins of enteropathogenic Yersinia. *J. Endocrinol. Investig.* **1988**, *11*, 139–140. [CrossRef]
152. Asari, S.; Amino, N.; Horikawa, M.; Miyai, K. Incidences of antibodies to Yersinia enterocolitica: High incidence of serotype O5 in autoimmune thyroid diseases in Japan. *Endocrinol. Jpn.* **1989**, *36*, 381–386. [CrossRef]
153. Polkowska-Pruszyńska, B.; Gerkowicz, A.; Szczepanik-Kułak, P.; Krasowska, D. Small intestinal bacterial overgrowth in systemic sclerosis: A review of the literature. *Arch. Dermatol. Res.* **2019**, *311*, 1–8. [CrossRef]
154. Bertalot, G.; Montresor, G.; Tampieri, M.; Spasiano, A.; Pedroni, M.; Milanesi, B.; Negrini, R. Decrease in thyroid autoantibodies after eradication of Helicobacter pylori infection. *Clin. Endocrinol.* **2004**, *61*, 650–652. [CrossRef]
155. Alipour, B.; Homayouni-Rad, A.; Vaghef-Mehrabany, E.; Sharif, S.K.; Vaghef-Mehrabany, L.; Asghari-Jafarabadi, M.; Mohtadi-Nia, J. Effects of *Lactobacillus casei* supplementation on disease activity and inflammatory cytokines in rheumatoid arthritis patients: A randomized double-blind clinical trial. *Int. J. Rheum. Dis.* **2014**, *17*, 519–527. [CrossRef]
156. Zamani, B.; Golkar, H.R.; Farshbaf, S.; Emadi-Baygi, M.; Tajabadi-Ebrahimi, M.; Jafari, P.; Asemi, Z. Clinical and metabolic response to probiotic supplementation in patients with rheumatoid arthritis: A randomized, double-blind, placebo-controlled trial. *Int. J. Rheum. Dis.* **2016**, *19*, 869–879. [CrossRef]
157. Podas, T.; Nightingale, J.M.D.; Oldham, R.; Roy, S.; Sheehan, N.J.; Mayberry, J.F. Is rheumatoid arthritis a disease that starts in the intestine? A pilot study comparing an elemental diet with oral prednisolone. *Postgrad. Med. J.* **2007**, *83*, 128–131. [CrossRef]
158. Huang, C.; Yi, P.; Zhu, M.; Zhou, W.; Zhang, B.; Yi, X.; Lu, Q. Safety and efficacy of fecal microbiota transplantation for treatment of systemic lupus erythematosus: An EXPLORER trial. *J. Autoimmun.* **2022**, *130*, 102844. [CrossRef] [PubMed]
159. Wartofsky, L. Combination L-T3 and L-T4 therapy for hypothyroidism. *Curr. Opin. Endocrinol. Diabetes Obes.* **2013**, *20*, 460–466. [CrossRef]