Research Article
Volume 6:2, 2021

Journal of Inflammatory Bowel Diseases and Disorders

ISSN: 2476-1958 **Open Access**

Small Bowel Intestinal Overgrowth (SIBO): A Gender Specific Hormone Disease

Edward Lichten*

Department of Obstetrics and Gynecology, Wayne State College of Medicine, USA

Abstract

In the past 20 years, a gastro-intestinal complex has emerged that has been tentatively linked to Small Intestinal Bacterial Overgrowth (SIBO). The symptoms of constipation or diarrhea, bloating and distress, even to the level of cachexia have been presumed to be from bacterial overgrowth of methane producing Achaea bacteria including Methanobacteriales oralis and Methanobacteriales smithii. However, the SIBO symptom complex that was initially reported to be responsive to rifaximin and neomycin antibiotic therapy has subsequently become more and resistant leaving both patients and treating physicians in a quandary. The author was asked to consult on 18 patients whom had disruptive gastrointestinal symptoms, positive SIBO breathe test and repeated failure to respond to courses of primarily rifaximin therapy. These patients were overwhelming female and fell into the newly described field of Gender Specific Medicine (GSM). The biomarker for decreased bioavailable testosterone is the Free Androgen Index (FAI) in both sexes. Serum dysregulation included the gambit of hormonal assays: hypothyroidism, Hashimoto's thyroiditis, menopause, male hypogonadism, adrenal fatigue and low levels of vitamin D3 (Cholecalciferol). These patients had an unexpected high incidence of gastrointestinal autoimmunity including pernicious anemia, hyperchlorhydria per the Heidelberg test and autoimmune gastritis. Treatment was naturopathic, non-gonadal hormonal and when all else failed, in systemic anabolic hormone replacement, patient improvement did not reach the 75 percent threshold required in the study. Therefore, the protocol of mixed anabolic steroid replacement was initiated subsequently.

This retrospective chart review, excluded 3 patients who had inadequate treatment course of less than 4-months, the remaining 12 of 15 had greater than 75% improvement of symptoms on anabolic therapy program. The program utilized the FDA available nandrolone, stanozolol and testosterone anabolic medications. Diet restriction and supplements were continued by the naturopathic physician for digestion, constipation and SIBO complaints. At the end of 12-months, all 12 patients remained off rifaximin or any other antibiotic, anti-fungal or anti-helminth agent and were satisfied with their significant improved quality of life with only 5 of 12 continuing on the anabolic therapy protocol.

The Cascade to Disease hypothesis described herein emphasizes environmental toxins/xenoestrogens as the trigger that leads to loss of homeostasis within the serum, loss of bioavailable testosterone, loss of Estrogen Receptor-β/Estrogen Receptor-α (ER-β/ER-α) ratio. Remission was not forthcoming until the addition of inexpensive anabolic hormones.

Keywords

Hormone • Small bowel • Intestinal overgrowth • Autoimmune

Introduction

The work of Pimentel [1] in identifying Archaea bacteria as a cause of Inflammatory Bowel Syndrome-Constipation (IBS-C) in SIBO parallels the work of Barry Marshall, MD, who linked the presence of H. pylori to peptic ulcers. However, bacterial resistance for H. pylori has developed at a rapid pace, leaving more than 30 percent of H. pylori patients worldwide resistant to standard antibiotic therapy [2,3]. Similar concerns of antibiotic resistance have been voiced to explain the failure of rifaximin and neomycin for SIBO infections as a variety of other antibiotics, treatments offer no real benefit; including ciprofloxin, ampicillin, metronidazole, gentamycin, chlortetracycline, and trimethoprim/sulfamerazine and polymyxin [4,5]. Pimentel [4] states even the indications for antibiotic use are only "fair." Other physicians doubt the treatment and the established breath tests altogether. Thompson [6] stated that there are no long-term studies of rifaximin that extend over 10 weeks. Chan [7] stated that "Rifaximin does not improve patients' reporting of gastrointestinal symptoms and hydrogen breath tests do not reliably identify who will respond to antibiotic therapy."

***Address for Correspondence:** Edward Lichten, Department of Obstetrics and Gynecology, Wayne State College of Medicine, 555 South Old Woodward Avenue suite #700 Birmingham, Michigan 48009, USA, Tel: (248) 420.8726; E-mail: edwardlichten@gmail.com*

Received January 29, 2021; **Accepted** February 12, 2021; **Published** February 19, 2021

As Bures [8] stated, "Therapy for SIBO must be complex, addressing all causes, symptoms and complications, and fully individualized. It should include treatment of the underlying disease, nutritional support and cyclical gastro-intestinal selective antibiotics. Prognosis is usually serious, determined mostly by the underlying disease that led to SIBO" [8]. As antibiotic treatments for both H. pylori and SIBO are increasingly becoming ineffective, other factors must be addressed that affect the host microbiota ecosystem if effective treatments will be offered. Researchers and physicians must seek a cause, a biomarker and an effective treatment for both SIBO constipation and SIBO diarrhea.

The author has raised the hypothesis that environmental toxins being xenoestrogens could affect the microfilaria that sit at the apex of the gastrointestinal microbiome [9]. Subsequent articles have found more support for environmental toxins changing the microbiota [10,11]. Could this be superseding the presumed bacterial cause of these GI diseases?

Since endocrine dysfunctional and autoimmune states are frequently seen with SIBO patients, the author raised the question, "Could the endocrine and autoimmune dysfunction be a contributing cause to SIBO?"

The author hypothesized that should the findings of endocrine and autoimmune dysregulation be apparent in the data collected, then correction of these endocrine and autoimmune disease states might also improve the signs and symptoms of the SIBO infection, thereby offering a new direction for causation and directions in treatment to this disorder.

Materials and Methods

The physicians identified 18 SIBO patients who had failed treatment with not only recurrent trials of various antibiotic regimens including rifaximin/neomycin, but also naturopathic and vitamin/mineral supplementation. These individuals reported having their Quality of Life interrupted by their gastrointestinal disease symptoms. Eight of the 18 had to discontinue

their fulltime employment due to SIBO; five were retired or unemployed. Supplements used during the 12-month review were listed (Table 1). Three of the 18 patients were eliminated from this review because the anabolic therapy had not been in place for 4 months, their records were incomplete or they were lost to follow up. Fifteen patients were included. Each had a face-to-face interview by both physicians and repeatedly questioning in review of their charts, laboratory tests, and follow up telephone interviews in preparation of this review.

Table 1. Nutraceuticals and supplements.

Nutraceuticals and supplements		
Betaine hydrochloric acid	AloeVera Olive Leaf Extract	Allimed™
Bilex™ Ox bile	Mastic gum	Neem Plus™
Digestive Enzymes	Aygestin23 Colloidal Silver	Vitamin B12, Vitamin B6 Vitamin D
Alka-Selzer™ Gold (sodium bicarbonate)	Boron/Boric Acid	Probiotic Proton Pump Inhibitors
	Pepto-Bismol™	

The protocol included:

1) The SIBO laboratory check list (Table 2)

2) The hormonal laboratory check list (Table 3)

3) Treatment protocol

Table 2. Sibo Laboratory Check List.

SIBO Breath Test (Lactulose Breath Test)	IBS serum check of the migrating motor complex	Pernicious Anemia Serum Antibodies and B12 levels
Heidelberg Test	CdT; Vinculin	Intrinsic Factor
Celiac Disease IgA-transglutaminase (IgA-TTG); deaminated gliadin (IgG-DGL)	Chronic Autoimmune Atrophic Gastritis	Intrinsic Factor Blocking Antibody
Gastrin serum assay	Gastric Cancer Screen (optional)	Intrinsic Factor Binding Antibody
Pepsinogen II	Esophageal-gastro-duodenoscopy (EDG)	B12 (cobalamin) serum assay

Table 3. The Hormonal Laboratory Check List.

Demograhics	**Environmental Toxin Exposure**	**Medications**
Height	Smoker	Thyroxine
Weight	Alcohol	Corticosteroids
BMI	Medications	Gonadal hormones
Birth Year	Proton Pump Inhibitors	
LABORATORY TEST	RANGE: WOMEN	RANGE: MEN
Complete Blood Count		
Metabolic panel		
Auto-immunity Profile		
Sedimentation rate		
Anti-nuclear antibody		
C-reactive protein		
Hemoglobin A1c		
Thyroid Profile		
TSH		
Free T3 (triiodothyronine		
Free Thyroxine (T4)		
Reverse T3 (triiodothyronine)		
Thyroid antibody		
Thyroid peroxidase antibody		
Fasting insulin		
DHEA-sulfate		
Cortisol AM		
Cortisol PM		
Vitamin D3 25-OH		
Parathyroid Hormone		
Sex Hormone Binding Globulin		
Free Androgen Index		
Total Estradiol		
Total Testosterone		
Progesterone		
Insulin Like Growth Factor-1		
Follicle Stimulating Hormone		
Luteinizing Hormone		
Prolactin		

The SIBO laboratory check list

The SIBO laboratory check list includes pertinent gastrointestinal and autoimmune testing (Table 2). Naturopathic and medical therapies were begun initially as hyperchlorhydria, hypochlorhydria; pernicious anemia and chronic autoimmune atrophic gastritis were discovered. Esophageal-Diagnostic Gastroscopy (EDG) was ordered in 3 women and one man.

The hormonal laboratory check list

The hormonal laboratory check list included evaluation of pertinent endocrine system laboratory tests: serum assays of pituitary, thyroid, adrenal, pancreatic, gonadal function and Vitamin D3 25-OH (Table 3). Sex-Hormone-Binding Globulin (SHBG was included and calculation of the Free Androgen Index (FAI) [12]. FAI addresses testosterone bioavailability. Normal FAI reference ranges by gender were those of Burke and Anderson [12] in 1972 in Denmark. IGF-1 range was taken from Bennett [13]. Therapeutic range was considered normal if it exceeded the mid-range. The range and mid-point of these serum assay values by gender and age are those of Quest Diagnostic Reference Laboratories. They were included in Table 3. Pertinent data set appears in Table 4: cross-referencing laboratory tests, medications and treatment course in Table 4 including:

Table 4. Autoimmune findings.

Disease	Number pts	Treatments	Dosage	
Pernicious Anemia	3	Methyl-B12	5000 mcg/IM/week	
Hypothyroidism	3	Porcine thyroid	60-180mg/day	Tri-iodothyronine 7.5 mcg-22.5 mg/day
Grave's Disease	1			
Hashimoto's thyroiditis	3	Porcine thyroid	60-180mg/day	Tri-iodothyronine 7.5mcg-22.5 mg/day
Menopause				
Hypogonadism				

1) Occurrence of autoimmune diseases,

2) Occurrence of medical diseases,

3) Laboratory tests, and

4) Medical treatments.

Medical treatment

Hormone therapy included ICD 10 Diagnosis Codes, doses and frequency of prescription medications, intramuscular injections of testosterone (men), injections of nandrolone (men and women), stanozolol (men and women) and methyl-cobalamin (B12).

Estradiol replacement by cream or patch was selectively prescribed to two women with menopausal or vaginal complaints.

Based on prior experience, the women patients were titrated from 10mg to 20mg of nandrolone intramuscular injection once to twice weekly. 40 mg was the maximum prescribed. Stanozolol was given as 10mg to 20 mg weekly injection or 25 mg weekly or bimonthly as an oral capsule. The protocol was directed to restore to homeostasis the bioavailable testosterone using the FAI biomarker; raising total testosterone and decreasing SHBG. In only one individual was it necessary to prescribe 25 mg of stanozolol twice per week to bring the SHBG down to so the FAI was restored to normal range.

Doing so, the protocol was fulfilled: maximizing the biomarker (FAI) corresponded with the patient's response to treatment, relief from symptoms while avoiding side-effects (hirsutism). Spironolactone 100 mg twice daily was utilized to prophylactically minimize hirsutism in women; one man used 25 mg of spironolactone orally daily. In only one patient was the medication temporarily discontinued due to her underlying medical problem of biliary cholangitis. Men were titrated from 40 mg to a maximum of 80 mg nandrolone in the weekly intramuscular injections in addition to their testosterone intramuscular dosage of 120 to 160 mg weekly injection.

Testosterone

Testosterone is the primary anabolic hormone of men and women. Maximal production occurs during late adolescents and young adulthood and then fades after 40-years of age. Women produce about two-thirds as much testosterone as same-aged men but, she aromatizes the testosterone to estradiol. Women will lose 80 percent of their testosterone and estradiol production in the years from 40 to 50. Testosterone acts by binding to the Androgen Receptor with an affinity 10-fold greater than estradiol. Ninety-eight percent of testosterone [14] is bond to sex-hormone-binding-globulin, a protein produced in the liver. Only unbound-testosterone is bioavailable and bio-active. Testosterone can be converted to Dihydrotestosterone (DHT) by 5-alpha reductase. DHT is responsive for acne, fluid retention and is more anabolic and androgenic than testosterone. Bio-available testosterone is moved through the Androgen Receptor (AR) into the cytoplasm to bind to the Estrogen Receptors beta and alpha (ER-βER-β. A small dose of 10 mg testosterone could be added to the weekly injection for women who failed to report improvement in mental focus, relief from depression and, improved libido. The integrated role of the Estrogen Receptors with inflammation is discussed separately.

Nandrolone

Nandrolone is the first derivative of testosterone. It does not aromatize to estradiol nor is it reduced by 5-alpha reductase to DHT so breast tenderness, acne and premenstrual symptoms rarely occur. Nandrolone's binding to Sex-Hormone-Binding-Globulin (SHBG) is only 5 percent of testosterone and its affinity for the Androgen Receptor is 3-fold greater than testosterone. Nandrolone displaces testosterone so high serum levels of testosterone will be recorded but, the women patients will rarely report hirsutism. Women report improved mental focus, muscle formation, exercise endurance and libido. Men report the same but, high dose nandrolone may interfere with ejaculation. Nandrolone is the most anti-inflammatory gonadal hormone.

Stanozolol

Danazol and stanozolol are closely related pharmaceutical medications derived from Dihydro-Testosterone (DHT). The metabolites are up to 200-fold more active than the parent chemical. Both may transiently raise serum testosterone levels but, at 6-months their mode of action is to suppress the liver production of Sex-Hormone-Binding Globulin (SHBG) by 80 percent.

Danazol is a weak anabolic steroid available in the United States since 1971 and an effective overall medical treatment for endometriosis in women and a number of autoimmune diseases including Lupus Erythematosus, Idiopathic Thrombocytopenia, and Hereditary Angioedema. Danazol treats other autoimmune disorders. Biochemically, by lowering the SHBG it raises the Free Androgen Index (FAI), the biomarker used in this study for most accurate measure of bioavailable testosterone in women.

Free androgen index

Bioavailable testosterone is testosterone that is not bound-to-sex hormone binding globulin. Burke and Anderson [12] noted this in 1972, but, physicians and researchers have not incorporated this factoid into their journal articles or their medical practice. Anderson [14] showed that 1 µg of ethinyl-estradiol, one-twentieth of a birth control pill, will suppress the bioavailable testosterone by 38%. The Free Androgen Index is the ratio of total testosterone to sex-hormone-binding globulin which is representative of estrogen and xenoestrogen influence. The Free Androgen Index (FAI) serves as the biomarker for the patients in this SIBO review.

Role of the androgen receptor

Disruption in lowering the Free Androgen Index shifts the serum from a relative Anabolic/Testosterone dominance to an Estrogen Dominance. Biologically, more xeno- and estrogen molecules are able to bind to the Androgen Receptor on the cell wall. More xeno- and estrogen molecules enter the cytoplasm and bind to the nuclear membrane Estrogen Receptor. The Androgen Receptor is the rate limiting step in the determination of Androgen or Estrogen Dominance.

The Cascade to Disease uses Mixed Androgen Treatment (MAT) to upregulate the FAI as the drug-related biomarker for hormonal treatment. This shifts the balance back to the homeostatic state of Anabolic Dominance.

Outcome

Ideal FAI levels as published by Anderson were compared to men and women's values at the initiation of therapy. The increase in FAI was correlated to the patients' signs and symptoms of recovery from disease and need for non-hormonal medications.

Scientific method

The author's gynecologic experience with danazol therapy for endometriosis, mastalgia, premenstrual syndrome, and menorrhagia flowed over to migraine [15], catamenia seizure, catamenia pneumothorax and then to Crohn's Disease [16]. Danazol was observed positively to impact these aforementioned diseases. Barbieri's thesis [17] in 1981 focused on the role of danazol to reduce sex-hormone-binding globulin. Burke and Anderson [12] in 1972 focused on the role of SHBG in controlling bioavailable testosterone. The Air Force Rand Hand study [18] noted that exposure to Agent Orange (dioxin and DDT) xenoestrogens raised SHBG.

With this information, Lichten in clinical trials systematically reviewed medications that would raise total testosterone and decrease sex-hormone-binding globulin. Testosterone raises total testosterone. Topical testosterone raises estradiol levels and SHBG. Therefore, testosterone is best given as intramuscular injection or an implant for men. For both, nandrolone displaces and releases testosterone from cellular loci. Stanozolol, danazol and to lesser extent, oxandrolone lower SHBG. The most effective form is intramuscular stanozolol injection. This is the formulation of the mixed androgen therapy used within this study protocol.

Results

The table listing previously prescribed antibiotic medications that potentially disrupted the microflora of the GI tract in SIBO resistant patients are noted (Table 5). The information was recorded beginning from the initial assessment and processed as a retrospective chart study at the 12-month follow up. In these resistant SIBO patients, the summary of their concurrent medical diagnoses, doses and forms of medications prescribed, benefits and side-effects are listed at the 12-months study endpoint (Table 4). If the patient had discontinued the anabolic protocol, the laboratory tests of testosterone, SHBG and FAI were listed when the patient was on therapy.

Naturopathic and non-gonadal hormonal medications remained in use in 9 of the 15 patients in the 12-month study. After exclusion of the original 3 patients, twelve of the 15 previous antibiotic- SIBO failures reported greater than 75% improvement during the 12-month follow up with this multiple discipline approach to treatments without antibiotics. 5 of the 12 patients were on the MAT hormonal protocol at the 12-month end of the study. The unexpected high frequent occurrence of autoimmune and hormonal non-gonadal diseases in this population appears summarized herein (Table 5).

Table 5. Prescription agents that disrupt the microflora of the GI tract.

Class Individual agent	# Pubmed.com references	# Patients in study on meds	# trials
Aminoglycosides	Neomycin	24	
Cepaholsporins-	1st Cefalexin	1	
	2nd Cefprozil	1	
	3rd Ceftriaxone	5	
Glycopeptides	Vancomycin	33	
Lincosamindes	Cleocin	18	
Macrolides	Biaxin	6	
Monobactams	Aztreonam	4	
Antiparasitic	Albendazole	0	
Nitrofurans	Nitrofurantoin	0	
	Xazolidinones		
	Linezolid	1	
Penicillin	Amoxicillin	23	
	Augmentin	5	
Quinolones	Ciproflaxacin	28	
Penicillin	Amoxicillin/ clavulanate		
Sulfonamides			
Trimethoprim	Selfamethoxazole	7	
Bactrim			
Tetracyclines	Doxycycline	9	
Drugs against mycobacteria	Rifampicin	110	
	Steptomycin	8	
Others	Chloramphenicol	6	
	Metromidazole	73	
	Nitazoanide	1	
Antifungal	Fluconazole	13	

The goal of the translational endocrine and naturopathic therapy was to reduce the thyroid antibodies, TSH, FSH and LH while increasing the DHEA-s, morning cortisol, baseline Vitamin D3 and IGF-1. The goal of anabolic therapy was to raise the total testosterone, lower the SHBG, and raise the FAI. All patients were followed closely for changes in blood pressure, weight, heart palpitations, fluid retention, breast tenderness, and side-effects and hirsutism.

Failure of therapy

One 74-year old cachexic male made some significant albeit temporary improvement after suffering from SIBO related diseases for more than 20 years and reported a 50 to 70 percent improvement in quality of life. The combination therapies with human Growth Hormone (hGH) increased his weight by 15 pounds, reduced his gastrointestinal symptoms but, he remained cachexic. As he continued to self-doctor his medications, he lost weight off the nandrolone/testosterone/stanozolol protocol and his overall course of therapy was not considered fully successful by the author's standards. One premenopausal woman showed pyloric dysfunction on the Heidelberg test and a normal EGD except for the finding of antral gastritis. She failed to improve on any and all therapies and was deemed a failure. One cachexic woman discontinued the therapy after one month. She failed to gain weight or find relief of her symptoms as she was resistant to all naturopathic and prescription medications. This was the group eliminated from the study. One adult female patient showed moderate improvement on anabolic therapy, but then developed tan stools and upper abdominal pain. She was treated as a case of primary biliary cholangitis with clinical pernicious anemia with 5000 mcg of methyl-cobalamin daily with dramatic clinical improvement. She had periods of very good control on a combination of hormonal, naturopathic and methyl-cobalamin medications, hormonal stability was difficult to establish but at 6-months was greater than 50 and at 12-months was greater than 75 percent. Her improvement and course on hormonal therapy is on-going. She and her husband consider her a great success so she is, for the purpose of this study, not included with the three failures listed above.

These four patients were treated empirically with albendazole [19] after failure of the protocol. The first three showed no signs of improvement. The fourth patient with the complexity of her case with biliary cholangitis was unsure. This is reported for completeness.

Discussion

Are antibiotic therapies bound to fail in both SIBO and H. pylori? Based on molecular subtyping and antimicrobial susceptibilities of diarrheal patients in China [20], it is expected that more of the gastrointestinal microbiomes will become resistant quickly as antibiotic resistance spreads. Antibiotic resistance to Campylobacter coli was noted in nalidixic acid (100%), ciprofloxacin (100%), levofloxacin (99%), tetracycline (94%), metronidazole (93%), erythromycin (61%), streptomycin (72%), gentamicin (59%), ampicillin (50%), and chloramphenicol (29%). Multidrug resistance was detected in 108 of 109 Campylobacter coli isolates. Eamonn Quigley, outgoing president of the American College of Gastroenterology and Professor of Medicine and Human Physiology at the National University of Ireland in Cork stated "we're seeing more resistance to some of the more conventional therapies in term of H. pylori eradiation" [21]. "This is of concern for both patient acceptance of treatment regimens and the cost as some of the drugs is quite new" [21]. Expect antibiotic resistance in the treatment of SIBO to increase likewise. In large meta-analysis studies, rifaximin is not superior to less expensive antibiotics. Already, resistance it is being seen in neomycin therapy [22]. Although unlikely for rifaximin, prospective data are needed." That is why naturopathic treatments with prebiotics and postbiotics [23] are being empirically and blindly supplied. No one to date has identified the SIBO cause, biomarker or treatment/cure per the Scientific Method.

The existence of autoimmunity

There are a number of autoimmune diseases that have been found to have a higher incidence of SIBO than in control populations. There are three groupings of autoimmune diseases that are diagnosed by serum assay and associated with SIBO:

1) Autoimmune disease in the gastrointestinal tract: pernicious anemia with anti-parietal cell antibodies and with anti-intrinsic factor antibodies. Chronic Autoimmune Atrophic Gastritis (CAAG) [24] may have some of the same antibodies in addition to elevated gastrin serum levels.

2) Organ specific autoimmune diseases such as Hashimoto's thyroiditis with anti-parietal and anti-intrinsic factor antibodies, that may

coexist with any other autoimmune diseases and have other tissue specific auto-antibodies, and

3) Systematic autoimmune diseases such as rheumatoid arthritis and lupus that may be associated with other either or both autoimmune diseases previously listed (with or without anti-parietal and anti-intrinsic factor antibodies). They may have general inflammatory markers such as sedimentation rate, C-reactive protein and general autoimmune test such as Anti-Nuclear Antibodies (ANA), Anti-Streptolysin O (ASO), antibodies to Angiotensin-Converting Enzyme (ACE), and Rheumatoid Factor (RF).

The serum assays and clinical data from these 18 chart-reviewed patients are representative of all three areas of autoimmunity. Firstly, autoimmune diseases of the gastrointestinal tract are well recognized. Pernicious anemia is an autoimmune disease that destroys the parietal cells. Deficiency of intrinsic factor, presence of intrinsic factor blocking and binding antibodies, and anti-parietal cell antibodies can be found in both pernicious anemia and Chronic Autoimmune Atrophic Gastritis (CAAG). Clinically, intrinsic factor is essential for vitamin B12 [24] absorption and severe deficiency leads to megaloblastic anemia and the potential for neurological consequences. CAAG patients have abnormal gastrin and Chromogranin A (CgA).

Treatment of both conditions is by intramuscular injections of cobalamin (B12) and iron to treat respectively B12 and iron deficiency anemia. There are inconsistencies of serum diagnostic testing and treatment. The bioidentical forms of B12 treatment available as methyl-, hydroxy- and adenosyl-cobalamin are preferred over cyanocobalamin [24]. Recommended dosages of B12 in clinical treatment vary widely from oral to intramuscular as shown in the literature. There is proven coexistence of Chronic Autoimmune Atrophic Gastritis (CAAG) and Hyperparathyroidism (PHPT) [25]. Since CAAG is four times more frequent in autoimmune hyperparathyroidism (PHPT) than in the general population, and the occurrence of PHPT is three-fold greater in CAAG than in the general population, the author and others suggest "a potential role for autoimmunity" [25].

While the autoimmune diseases of the gastrointestinal tract consistently show anti-parietal antibodies and anti-intrinsic factors, these antibodies are present in endocrine and autoimmune diseases outside of the gastrointestinal tract. Such diseases include primary hyperparathyroidism (PHPT) [25], Type I diabetes [26], latent autoimmune diabetes [27], autoimmune thyroid disease [28], atrophic gastritis with AT [29], vitiligo [30], celiac [31], recurrent aphthous stomatitis [32], pangastritis [33], lupus erythematosus [34] and multiple sclerosis [35]. Secondly, these endocrine and autoimmune states, such as diabetes, have comorbidity with other autoimmune disease states. Type I diabetes characterized by the autoimmune loss of insulin-producing pancreatic βcells exhibit an increased risk of other autoimmune disorders such as Autoimmune Thyroid disease (AT), Addison's disease, autoimmune gastritis, coeliac disease and vitiligo [36,37]. Vitiligo patients [38] and their relatives have increased frequency of anti-thyroid microsomal, anti-parietal cell and anti-adrenal autoantibodies. This highlights the strong genetic contribution [38]. These autoimmune organ diseases respond to individual therapy: insulin replacement for diabetes, thyroid replacement for autoimmune thyroid disease and anti-inflammatory medications for lupus. Treatment of one of the individual diseases does not improve the other autoimmune medical conditions. Thirdly, not only do these endocrine and autoimmune disease states have higher incidence of comorbidity with other endocrine -autoimmune states (previously called Polyglandular Autoimmune Syndrome Type II (PSAS Type II)) [39-41] but, the diseases are systemic: rheumatoid arthritis, Sjögren syndrome, and systemic lupus erythematosus for example. Fallahi [28] found all three types of autoimmune disorders could exist in the same population. He suggested that patients with AT who remain unwell, or who develop new non-specific symptoms (despite adequate treatment) should be screened for other autoimmune disorders [28]. Vrkljjan [41] suggested that the diseases (pernicious anemia, primary hypothyroidism, and Addison's disease) "share the same etiological factors but also overlap in pathophysiology and clinical characteristics favors older classifications of APS which consolidate all endocrine and other organ specific autoimmune diseases into one category" [34]. Wielosz [40] instituted immunosuppressive therapy in autoimmune polyglandular syndrome which reduced the symptoms of connective tissue disease.

The conclusion reached is that SIBO is an autoimmune disease, is associated with other autoimmune diseases and should respond to treatments that are generally effective in autoimmune diseases. Many of these autoimmune diseases have a female predominance. Female predominance is a commonality of Gender Specific Medicine.

Gender specific medicine

Zampetti [27] made an association missing from all previously referenced articles on the interrelationship of 1) autoimmune disease of the gastrointestinal tract, 2) autoimmune disease of specific organs and 3) systemic autoimmune disease. He referenced the word gender, Gender Specific Medicine or Molecular Mimicry. It has been hypothesized that "functional disorders such as irritable bowel syndrome, chronic fatigue syndrome and anorexia nervosa are caused by auto-antibodies to neuronal proteins induced by molecular mimicry with microbial antigens" [42]. For 40 years, some have hypothesized that pooled immunoglobulin and elimination of the bacteria from the microbial flora that express the cross-reacting antigens should be possible [43]. The literature repeatedly demonstrates that treating the autoimmune disease, whether it be pernicious anemia [44] or hypothyroidism [45], can clear the SIBO.

Clearing the SIBO does not improve the underlying autoimmune disease nor do antibiotics offer any consistent, long-term solution [46]. Stockbruegger [47] and Ngo [48] offer an alternative hypothesis to the cause of autoimmunity that rejects molecular mimicry.

They hypothesize that the overlap of bacterial overgrowth and autoimmune disease depends on: 1) altered immune conditions [46]; 2) gender [48]; genetics and 3) exposure to external factors [11] (i.e., hormones) and the subsequence response to such factors might influence susceptibility to autoimmune disease [46]. The altered immune conditions in these patients has been extensively noted by Ngo [48] at macrophage, T cells, cytokines, interleukins and natural killer cell levels. He notes that the differences in immunology function can depend on the gender and age of the individual. The gender of the host dictates the basic normal levels of Gender Specific Hormones. SIBO and certain autoimmune diseases such as pernicious anemia, autoimmune thyroiditis, and systemic diseases such as lupus erythematosus, rheumatoid arthritis and multiple sclerosis share a gender predilection of female: male of 3:1 or greater. This 3:1 ratio only persists during the reproductive years; 15 to 50 years of age. This gender deferential is not pronounced in either the pediatric or elderly population.

Gender specific medicine and biomarkers

The free androgen index and estrogen receptors: M. Legato, Professor emeritus of cardiology in NY Columbia Hospital, has developed a unique specialty in the field of medicine called Gender Specific Medicine [49]. She has focused how differences in gender affect the prevalence and penetrance of disease. Examples of such observations are the 3:1 incidence of lupus erythematosus in women. Van Vollenhoven, [50] chairman of medicine at Stanford, made the observations in 1994 that "Estrogen, Progesterone and Testosterone: can they be used to treat autoimmune disease?" McGuire used danazol, a weak anabolic steroid to treat lupus erythematosus symptoms.

JL McGuire's hypothesis contains three elements:

1) Autoimmune disease

2) Coexistence with Gender Specificity

3) Signs and symptoms improve with danazol, an anabolic steroid.

The point to be made is that diseases that are chronic, inflammatory and show improvement with anabolic steroids are in fact autoimmune. SIBO, Crohn's Disease [51,16], lupus, migraine [15,17], endometriosis [18,52], Idiopathic thrombocytopenia purpura, Hereditary angioedema, and

diseases in general that respond to danazol retains this commonality of Gender Specific Medicine. Gender is an important missing link [53].

The literature reports that testosterone, another anabolic steroid, can reduce the autoimmune state of Crohn's Disease [51,16]. "Low serum testosterone is associated with an increase in inflammatory factors, while testosterone administration reduces them. There is evidence for an immunomodulatory effect of testosterone on differentiation of regulatory T cells" [51].

Nandrolone has more profound anti-inflammatory effects than testosterone [54]. These independent observations are linked in the step-to-step Scientific Method hypothesis outlined in the Cascade of Disease presented herein (Table 6) [55-58].

Table 6. Gender Specific Medicine integrates within the Cascade of Disease hypothesis.

Cascade of Disease	hormones related	
1) Epigenetic Causation	XE: toxin environmental exposure [52]	Independent of genetics
2) Neuro-endocrine Dysregulation	Hypothalamic-dysregulation leading to decreased testosterone production [55]	
3) Decrease Biomarker/Fai Free Androgen Index	Xenoestrogens (XE) increase SHBG production [18]	
4) Androgen receptor become estrogenic dominant	Allows more estradiol and XE to enter the cell [56]	
5) Decreased Er-B/Er-A Ratio Intracellular Biomarker	Loss of Estrogen Receptor B/ alpha ratio. ER-beta responds to raising serum testosterone [56].	
6) Restore Normal Fai Biomarker	Lichten: migraine [15] Lichten: IBM [16] Lichten: Endometriosis [57,58] Lichten: SIBO	
7) Restore Health	Will the ER-beta/ER-alpha normalize as well?	Unanswered Question

Future knowledge and research in SIBO and IBD

The gastrointestinal argument of molecular mimicry is unsupportable through the Scientific Method as the review exposes herein. Each of the steps in the Cascade to Disease is a disproof of the molecular mimicry arguments. However, there is no question that the environmental toxins change the bacterial flora [10,11] and are secondarily, albeit, an important contribution to the disease process.

The reports of Pierdominici [56] have added the missing element in the hypothesis delineated here: measurement of the Estrogen Receptor beta and alpha ratio [40]. They showed that the reduction of the ER-beta/alpha was identified in individuals in active flairs of Crohn's Disease. The ER-beta signalling controls the autoimmunity activity of IL-6 [51].

The anabolic hormone controls the immune cytoplasm signalling. There is no molecular mimicry element that affects the Estrogen Receptor beta and alpha. The author's research is on-going: the intent is to integrate the observations of the Estrogen Receptors and cytoplasm interleukins, cytokines, a, TNF and Thymus factors with the Cascade to Disease steps delineated [59].

Conclusion

This retrospective chart review analysis is the first to document the utilization of anabolic steroids in a rifaximin- antibiotic resistant SIBO population. This data supports the findings that the altered immune serum laboratory findings associated with SIBO and comorbid autoimmune diseases can be influenced by Gender Specific Hormones. Treatment with anabolic steroids that correct the bioavailable testosterone (FAI) can improve the signs, symptoms and autoimmune biomarkers of these Gender Specific Medicine diseases of which SIBO is one.

The Scientific Method serves as proof that the Cascade of Disease links Gender Specific Method, McGuire's Hypothesis, and observational reports of the benefits of anabolic steroids. Anabolic Hormones are effective and supportive treatment regimen of SIBO, IBD and autoimmune diseases. The Free Androgen Index (FAI) proves to be a key reproducible biomarker for diagnosis, recovery and follow up of not only resistant cases of SIBO but, also other autoimmune disease states.

Missing from the SIBO literature but present in the IBD literature is the Hypothalamic-Pituitary-Gonadal axis dysregulation that precedes the findings of low bioavailable testosterone identified in our patient population. Missing in SIBO research is the measurement of Estrogen Receptor-beta/Estrogen Receptor-alpha, Androgen Receptor dysregulation and cytoplasm antibody changes. The authors expect that future researchers will find that the observations in SIBO predicted in the Cascade of Disease will be identical to those previously observed with Crohn's Disease.

The anti-inflammatory activity of anabolic steroids is well known. Nandrolone and testosterone both have direct effects on Natural Killer cells (NK) interleukins, thymus serum factor and IL-1 production mediated by macrophages. This may explain why nandrolone was effective in these autoimmune cases, not dissimilar to the attempt by Wielosz to use anti-inflammatory agents to treat autoimmune polyglandular syndrome. This study confirms that in adults, normalizing the Gender Specific Hormone biomarker measurements of bioavailable testosterone, i.e., the Free Androgen Index (FAI) with nandrolone and stanozolol can have a positive, remission driven application to select autoimmune diseases which includes SIBO.

In summary, SIBO is a Gender Specific Medicine, autoimmune disease which can be treated effectively with anabolic steroids that reset the identifiable hormone dysregulation probably caused by xenoestrogen exposure. Never-the-less, resetting normal bioavailable testosterone level may offer effective treatment for both SIBO antibiotic failures and for supporting the underlying autoimmune disease. The more pronounced increases in the serum biomarker FAI strongly correlate with improvement in the patient's symptoms in this chart review.

All these autoimmune diseases may be just one epigenetic disease. While medical science is unable today to change genetics, Gender Specific Medicine Treatment does propose to revert the Estrogen-Dominance at the Androgen Receptor back to Testosterone-Dominance with anabolic therapy. The clinical course of anabolic steroids can normalize the biomarkers and bring a reversal to the Cascade to Disease in SIBO as it has in Crohn's and other inflammatory diseases.

Scientific proof herein supports the paradigm expansion of medical investigation and treatment of SIBO alone and autoimmune diseases in general to include Gender Specific Medicine, hormonal evaluations, anabolic therapy and the routine use of the biomarkers (FAI, ER-β/ER-α). Only then can the medical profession offer the scientific basis for disease causation, use of biomarkers and thereafter, the potential for recovery and remission.

Appendix

Response to anabolic hormonal therapy: In the 15 patients followed for 12-months, all 3 men and 10 of 12 women showed 3 to 10-fold elevation of the SHBG associated with abnormally low FAI based on the ideal range on Anderson. The women were treated with nandrolone and stanozolol by weekly intramuscular injections. When the patients complained of painful injections, they were shifted to oral stanozolol starting at one capsule weekly. The 3 men with low FAI had evidence of hypogonadism/low testosterone (male) defined by elevated serum assays FSH/LH. Testosterone was added to the previously described nandrolone and stanozolol for men. Of the 12 women, 3 cases of menopause (female) were identified as these 3 had

elevated serum assays of FSH/LH and low serum total estradiol. When menopausal symptoms were still present after initiating nandrolone, they were treated with add back estradiol topical or transdermal patches. There were 6 cases of hypopituitarism defined by IGF-1 below ideal range of RM Bennett MD for fibromyalgia. Five patients were prescribed human Growth Hormone (hGH) after having good but incomplete relief with anabolic therapy. Three found the medication beneficial and continued the therapy. Two men and one woman returned to full employment. The remaining individual was the 74-year old cachexic male considered a failure of therapy although some improvements over all were noted. The remaining female individual discontinued the medication due to cost. An L-arginine stimulation test was ordered for each of the patients continuing therapy. One presumed case of primary biliary cholangitis was seen by the author's request at a major University Teaching Hospital in Boston. The patient's right upper quadrant pain dissipated on 5000 mcg of methyl-colbamin intramuscularly every day and subsequently reduced to 5000 mg every other day. The tan stools remained but therapeutic treatment with ox bile; methyl-colbamin and anabolic therapy dramatically improved her quality of life. Two patients had positive findings of Antinuclear Antibody (ANA) titres of 1:160 that fluctuated to 1:80 on anabolic treatment. This was considered normal range variation, but, the presence of positive ANA was noted in the findings of autoimmune disease states in 2 of these 18 patients.

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How to cite this article: Lichten, Edward. "Small Bowel Intestinal Overgrowth (SIBO): A Gender Specific Hormone Disease " *J Inflam Bowel Dis Disor* 6(2021): 141.