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Five Anabolic Steroids in the Treatment of Inflammatory Bowel Disease

*Edward M Lichten, MD**

Former, Assistant Clinical Professor, Wayne State College of Medicine, USA

Abstract

Crohn's disease (CD) and ulcerative colitis (UC), the constituents of Inflammatory Bowel Disease (IBD), are the most destructive benign diseases of young adults. Two-hundred thousand young men and women in North America will have major bowel resection annually, half to experience a premature death and many an increased risk of colorectal cancer. New cases in the youngest quadrille are appearing at a 0.5 percent rate per year. Adalimumab, the last pharmaceutical TNF-inhibitor drug approved for IBD was 17 years ago. Adalimumab's failure rate is 40 percent by year two, 60 percent by year five, and the 12-year German study questions whether there is any long-term gain in quality of life at all. The problems to date in understanding and treating IBD are that no one has identified the cause, no specific biomarkers are recognized, no alternatives to overtly toxic medications and no alternatives exist for inevitable surgical resections.

That has changed. There are now serum hormonal biomarkers that are highly predictive of flairs in Crohn's diseases; the first being the nuclear membrane Estrogen Receptor-beta/Estrogen Receptor-alpha ratio. The second being bioavailable testosterone measured as the Free Androgen Index. Causation is clearly demarcated to hormonal dysregulation at the Hypothalamic-Pituitary-Gonadal Axis suppressing testosterone production. Five inexpensive, generic, FDA approved anabolic steroid medications have been successfully used to treat IBD, albeit, not the recognized standard of care.

Here is the future of medicine: After initial medical information intake, measure Gender Specific Medicine biomarkers of gonadal hormones (causation) and then treat to normalize these biomarkers. Admixtures of anabolic steroids should reset the biomarkers and reduce the autoimmune, inflammatory, and systemic aspects of disease. Remission may be attainable with even the most resistant Crohn's and Ulcerative Colitis patients as observed in the Case Reports.

Background

Gender Specific Medicine started as an observational medical subspecialty that traverses all fields of health care. The gynecologists, as Gender Specific Medicine specialists for women, noted a profound 100-fold increase in the Estrogen Receptor-β/Estrogen Receptor-α ratio [1] in proliferative endometriosis tissue. Not until the gastroenterologist realized that a decrease in the ER-β/ER-α ratio strongly correlated with flairs in Crohn's Disease [2,3] did the significance of the Estrogen Receptors take hold of the Gender Specific Medicine hierarchy. The ER-β/ER-α ratio has become one of the two key biomarkers for physicians and researchers to identify, analyze, and treat within this Gender Specific Medicine (GSM) specialty. For Gender Specific Medicine (GSM) now supersedes symptomatic treatments such as adalimumab in Inflammatory Bowel Disease, leuprolide acetate in endometriosis and corticosteroids in many autoimmune diseases, because GSM addresses causation.

ER-β/ER-α is a highly specific biomarker for inflammation that can be measured in the T-lymphocytes in the blood. Bioavailable testosterone [4] is necessary for normal function of the Androgen Receptor (AR), Estrogen Receptor (ER) and aromatase activity. Bioavailable testosterone is measured in the serum as the Free Androgen Index [5] (FAI); the ratio of total testosterone (TT) to sex-hormone-binding globulin (SHBG). There is gender difference: The ER-β/ER-α ratio is strongly elevated in endometriosis [1] and depressed in IBD [2,3]. These ratios are still untested in the majority of disease, but, they are expected to be depressed in both men and women with cardiovascular disease, adult diabetes and other chronic diseases that have relatively equal distribution between men and women [4]. The ER-β/ER-α ratio is expected to be elevated in diseases that have a predilection for women such as Lupus Erythematosus [5] and breast cancer [6]. How the con-

***Corresponding author:** Edward M Lichten, MD, Former, Assistant Clinical Professor, Wayne State College of Medicine, 555 South Old Woodward Avenue Suite #700, Birmingham, Michigan 48009, USA, Tel: (248)-593-9999

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current serum measurements of FAI [7,8] will correspond to the ER-β/ER-α ratio may be still one of conjecture, but, based on the medical knowledge gained in research, it is expected that a decreased FAI level will correspond directly to the ER-β/ER-α ratio.

"Gender Specific Medicine bridges the gap between the past and future of medicine", stated Marianne Legato [9]. Instead of limiting medical treatment to symptoms in IBD with non-specific anti-inflammatory's drugs such as azulfidine, corticosteroids, and disease-modifying anti-rheumatoid drugs (DMARDs), Gender Specific Medicine is evidence-based medicine redirecting physicians in the single-mindedness of first treating causation. Treatment of inflammation cannot dismiss gender, gonadal hormones, and cytoplasm immunochemistry. As Legato clearly points out, "phenotypically, women have twice the incidence of Crohn's disease, four times the incidence of gallbladder disease, five times more irritable bowel and 20 times more functional bowel disease: How can hormones not be intimately involved in disease?" [7].

JL McGuire [10] predicted 25-years ago that gonadal hormones will be proven effective in treating autoimmune disease. His 1994 article was entitled "Estrogen, progesterone, and testosterone: Can they be used to treat autoimmune diseases?" He used the anabolic steroid danazol to treat Lupus Erythematosus. A more encompassing discussion of the five, FDA approved anabolic steroids and their properties appear in the section entitle Method Table 1.

More than mere conjecture, epidemiologic, observational, and epigenetic studies link the exponential increase in inflammatory diseases to the exponential increase in manmade environmental chemical exposure. Diseases such as IBD are mediated by changing in the hormonal milieu [11]. Oral contraceptive use increases the risk of both Crohn's and ulcerative colitis disease by approximately 30 percent [12]. Phthalate exposure in utero shortens the anogenital distance [13]. Sperm counts have fallen 75 percent worldwide since 1950 [14]. There is no question that mankind is being subjected to chemical insults.

The author's hypothesis includes three components:

1) Xenoestrogens (manmade hormones) may initiating the cascade into inflammatory disease, by

2) Triggering observed hormonal dysregulation in bioavailable testosterone production, and

3) McGuire's hypothesis: Correcting the bioavailable testosterone biomarker with anabolic steroids may effectively reverse disease.

Health it seems, is dependent on the anabolic hormonal milieu. Table 2 offers a schematic of the complete hypothesis. The peer reviewed literature offers references supporting these previous observations. The Case Reports are considered part of an initial pilot study of feasibility and safety. These FDA pharmaceutical agents significantly improved patients' well-being, supporting further Gender Specific Medicine Research.

Table 1: A more encompassing discussion of the five, FDA approved anabolic steroids and their properties.

Generic/Brand/ year FDA approved	Occurrence: *in vivo* = natural- *In vitro* = manmade	Preparation	Medical journal article	Biochemistry: Raises FAI. Lowers SHBG.
Anavar® Oxandrolone 1964	Synthetic AR-agonist	Oral	[29]	Raises FAI, testosterone. Lowers SHBG.
Danocrine® Danazol 1972	Synthetic AR-high affinity	Oral	[30]	Raises FAI. Lowers SHBG. Binds SHBG displaces TT; 44% aromatase inhibitor
Deca-durabolin® Nandrolone 1962	natural	Intramuscular	[31]	Raises FAI. Raises testosterone by displacing from AR
Testosterone 1939	natural	Intramuscular, oral, topical	[32]	Raises FAI. Raises testosterone directly; may lower SHBG if not topical
Winstrol® Stanozolol 1982	Synthetic AR-high affinity ER-agonist	Oral, intramuscular	[33]	Raises FAI. Lowers SHBG. only 5% bond SHBG

Table 2: Proposed sequences of events from xenoestrogen to immune reaction.

Gender Specific Hormone	Serum Level			
Endocrine Disrupting chemical - xenoestrogen	*Suppress natural*			
	Hypothalamic Pituitary Gonadal Axis	*Suppress natural* Total Testosterone from gonad		
				Together Suppress bioavailable
Endocrine Disrupting chemical - xenoestrogen		Increased SHBG production		Testosterone

Table 3: Proposed sequence of events: Bioavailable testosterone to inflammatory immune response.

Bioavailable Testosterone Normal	Androgen Receptor	Estrogen Receptor beta stays homeostatic		Cytoplasm response Anti-inflammatory
				Bioavailable Free Androgen Index
Bioavailable Testosterone abnormal (lower) creating a state of Estrogen Dominance	Androgen Receptor	Estrogen Receptor alpha signaling favors inflammation		Cytoplasm response is inflammatory

Method

The author identified patients who had been diagnosed elsewhere with IBD by colonic biopsy and had unsuccessfully been treated with medication and/or surgery. There were four men and two women who remained in treatment for more than one year. The women avoided pregnancy and used barrier methods for contraception. The men had normal prostate examinations, normal prostate specific antigen and had no history of prostate and/or testicular cancer. There were no contraindications to the anabolic therapy. Each underwent a comprehensive laboratory assessment described previously [15]. Note was made of where the women were in their menstrual cycle, time of day of laboratory assessment, and any previous history of manmade or natural hormonal therapy including use of contraception.

Biomarker

The Free Androgen Index was used as the biomarker for bioavailable testosterone. Anderson [7] (1972) described the FAI as the ratio of total testosterone to sex-hormone-binding globulin. He noted that 98 percent of testosterone is bound, the majority to SHBG, making only 2 percent unbound or bioavailable. Slight changes in SHBG dramatically affect the bound-testosterone-to-SHBG quantity; just 1 ug of ethinyl estradiol will decrease bioavailable testosterone [8] by 38 percent. All estrogens increase SHBG: Estriol during pregnancy can increase the SHBG concentration from 50 nmol/l to 750 nmol/l. One milligram of conjugated equine estrogen [16] increases SHBG by 45 percent while naturally occurring 17-β estradiol has little effect on SHBG. Fish and the Air Force Ranch Hand [17,18] study showed xenoestrogens increase SHBG (Table 3).

Protocol

The patients must be kept on a 6-week course of prednisone and weaned off to prevent an inadvertent flair. Having drawn the complete blood count, metabolic panel, sedimentation rate and components of FAI initially, all serum assays are repeated at 6 to 12-week intervals depending on the clinical course of the disease.

The initial treatment protocol for women with IBD started with standard dosage for women with endometriosis: 100 mg three times daily; maximum dosage used could be as high as 400 mg three times daily. The patient's metabolic panel was repeated at 3-month intervals to avoid inadvertent changes in liver enzymes. The FAI increased on danazol as documented in the literature: 2 to 3-fold within 6 days to 8 weeks. If symptoms did not dramatically improve, then the course of therapy was changed: First by increasing the dosage of danazol and secondly by shifting to nandrolone and stanozolol.

The combination of nandrolone and stanozolol parallel the clinical effects of danazol, albeit, 4 to 20-fold [19] more potent. Total testosterone increases from less than 50 ng/dl to upwards of 300 ng/dl. SHBG drops to less than 50 nmol/l. If doubling the dosage of nandrolone and stanozolol was not effective in relieving symptoms, additional therapy with oxandrolone 1.25 to 2.5 mg is a daily was prescribed.

Men are prescribed parenteral testosterone in dosages of 80 to 120 mg intramuscularly (IM) per week. The dosage

may be doubled in severe cases. Implanted testosterone pellet dosages are 600 to 800 mg every 8 to 12 weeks. To this, nandrolone 40 mg IM once or twice per week and stanozolol 10 to 25 mg per week IM are added. If needed, oxandrolone 2.5 to 10 mg daily is added to the men. For the most severe cases that were not responsive to purely anabolic therapy, human growth hormone at 0.1 mg subcutaneously was added daily.

Anabolic hormones

There are 6 anabolic hormones that are FDA approved and available in the United States. The authors do not use methyl-testosterone except rarely to treat women with menopause and vaginal atrophy because of the high incidence of hirsutism. The remaining five are the subject of this clinical and retrospective literature review.

Danazol has been available as a commercial FDA approved product since 1971, primarily for women with endometriosis [20] disease, heavy menstrual [21] bleeding, migraine [22], mastalgia [23], and premenstrual syndrome [24]. The side-effect of hirsutism may be minor, dose related and treatable with spironolactone. Barberi [20] has produced a classic monolog on the multitude of biological and chemical reactions induced by danazol. Danazol as a weak androgen will raise testosterone levels slightly for 3 to 6 months. Its primary action is to suppress SHBG production in the liver. The FAI increases by two to three-fold [20]. Gynecologists have use danazol for extended periods of time. The author treated a woman with catamenial epilepsy with danazol in doses up to 1200 mg daily for 30 years without incident [21].

Testosterone, danazol and oxandrolone are pharmaceutically manufactured and available at neighborhood pharmacies: Nandrolone and stanozolol are no longer available from commercial pharmaceutical manufacturers but are available through state approved compounding facilities. Testosterone cypionate is intended for intramuscular use; testosterone pellets are implanted. Note that only parenteral use is applicable because topical testosterone aromatizes to estrogens and raises SHBG. Parenteral use does not. Dosage of testosterone cypionate is 80 to 120 mg IM/per week for men; the dose may be doubled for the most ill. Testosterone is rarely used in women due to hirsutism; typical dosage may be 10 mg IM/ per week. Due to the 3-day half-life, most patients use intramuscular injections twice weekly.

Nandrolone is the first derivative of testosterone. It is the key anabolic preparation being 3 times more anabolic than testosterone and only bound minimally to SHBG. Nandrolone neither aromatizes to estrogens nor is reduced to dihydrotestosterone making this the preferred anabolic hormonal therapy for women. Nandrolone will displace testosterone from the Androgen Receptor-b because of its greater affinity for the AR loci receptor. In men, the dosage of nandrolone is kept at less than half that of testosterone so as to not interfere with erectile performance. Dosage in men is 20-80 mg IM/per week; women dosages are 20 mg IM, once to twice weekly.

Stanozolol is chemically quite similar to danazol. Both pharmaceutical drugs are derivatives of dihydrotestosterone. Stanozolol's primary function is to reduce the liver production of SHBG [25]. It is 100 times more potent milligram for milligram than danazol: 2 mg oral stanozolol three times daily equates to 600 mg of oral danazol daily. Intramuscular dosing of stanozolol is limited to 10 to 25 mg per week. SHBG is reduced by 80 percent [25] in weeks; the maximum effect may be seen in less than 6 to 8 weeks. Stanozolol due to its greater affinity for the AR loci may also displace testosterone increasing its anabolic potential. Due to the lower dosage, hirsutism and liver enzymes effects are less likely with injectable stanozolol.

Oxandrolone is a synthetic oral anabolic steroid with more anabolic and less androgenic potential. It does reduce SHBG [26], but not to the predictable magnitude of stanozolol or danazol. It does displace testosterone from the AR receptor and is not significantly bound to SHBG. Commercially produced, the tablets are available in 2.5 mg. Women's dose begins at 1.25 mg daily and for men at 2.5 mg daily. Oxandrolone in low doses rarely increases liver enzymes; the metabolic panel is followed quarterly with the FAI, and Complete Blood count. Higher doses may be more problematic.

Table 4: Patient demographics.

Gender	Age dx	Years of MAT	Medicine/ surgery	FAI initial [TT]*100*.033/[SHBG]	FAI high point	Mixed androgen therapy	Improved
EN CD male	31	5	Short bowel	FAI = 31%	FAI = 397%	T, N, S, hGH, O	> 75% while on MAT
JC CD male	35	5	Short bowel; ileostomy	FAI = 8.6% FAI = 212*3.3/ 86	FAI = 376% FAI = 571*33/25.9	T, N, S, hGH, O non-compliant	> 50% while on MAT
BT UC male	17	4	Ileostomy	FAI = 47.7% FAI = 593*33/41	FAI = 83% FAI = 454*3.3/18	T, N, S non-compliant	> 75% while on MAT
NM CD male	8	2	No surgery	FAI = 57% FAI = 446*3.3/29	FAI = 838% FAI = 1778*3.3/7	T, N, S, hGH, O	none
TB CD female	14	4	No surgery	FAI = 0.5	FAI = 8.9 FAI = 271*3.3/10	Danazol, N, S	> 75% while on MAT
AS CD female	12	1	No surgery	FAI = 0.4 FAI = 11*3.3/81	FAI = 20.9 FAI = 63*3.3/10	N, S, hGH non-compliant	> 75% while on MAT

Monitoring

While danazol can affect a 2 to 4-fold increase in the FAI from baseline in women, the nandrolone-stanozolol combination can increase the FAI by 10-fold in men and up to 40-fold increase in women [19]. Increase in the FAI or lack thereof, may predict the difference between success and failure. Increases in the FAI do not guarantee remission, however, as these are multi-factorial and complicated disease states.

Results

The Case Reports appear in Table 4.

Men on the triple combination of testosterone cypionate, nandrolone and stanozolol can have a 6-fold to 10-fold increase in the FAI over baseline. EN had a 10-fold increase and went from being medically disabled to completing a master teaching program and employment. NM had a 15-fold increase in FAI remains barely was able to maintain himself out of the hospital. The dosage of anabolic therapy is reduced once the patient's medical status has stabilized as it did for EN. The normal FAI set by Anderson was 0.7 to 4.0 (70% to 400%). The dosage of anabolic therapy for EN was reduced when his FAI reached 3.97 because even with his Short Bowel Syndrome, he went from being anemic to requiring phlebotomy for polycythemia secondary to his parenteral testosterone dosage.

Non-compliance has been the problem with JC and BT. When they followed the protocol, their sedimentation rate, C-reactive protein, and bowel complaints were reduced.

Patient TF was initially seen at age 23; she had an initial two-year period of success with danazol only to flair on a TV weight loss diet. She tolerated the shift to nandrolone and stanozolol for an additional 18 months, stopped therapy, conceived and delivered a healthy girl vaginally. There were minor flairs after delivery and in the year of breast feeding. Based on the FAI, she was been encouraged to resume the anabolic therapy.

Patient AS was initially seen at 22-years of age in a pre-morbid state: Three peritoneal drains, wheelchair bound, TNF-inhibitor failures with multiple drugs and refused surgery because of being such a poor candidate. She was treated with the nandrolone-stanozolol injections twice weekly and human growth hormone. She gained 27 pounds in 16 weeks, had the drains removed and returned to work only to stop all therapy to see a natural healer. She reverted to her premorbid state within 6 months. Compliance again was an issue.

Discussion

Based on the Scientific Method, the aforementioned hypothesis, background information, research and observed results establish the three elements of the hypothesis as a proven theorem. Xenoestrogens offer a credible explanation for the observation of Hypothalamic-Pituitary-Gonadal axis dysregulation; xenoestrogens increase SHBG, offering a credible answer to the observed decrease in bioavailable testosterone and increase in SHBG. Together, the observed decrease in bioavailable testosterone shifts the host toward "Estrogen Dominant". The FAI serves as the biomarker for the gross changes occurred to this point.

Androgen and estrogen receptors

It is clear that only the unbound, bioavailable testosterone can affix to loci in the Androgen Receptor on the cell wall. The increased presence of SHBG and decreased total testosterone production works against the host maintaining anabolic homeostasis. When xenoestrogens are 'added-to' [epi] to the individual's genetic makeup, they induce abnormal mRNA and DNA which propagate inflammation and disease. Xenoestrogens, heavy metals, and synthetic and conjugated equine estrogens increase SHBG; they work in concert to diminish the bioavailable testosterone, measured as the FAI. Directly, xenoestrogens affixing to the AR loci are transported into the cytoplasm of the cell and to the Estrogen Receptor and signal inflammatory responses.

The Androgen Receptor serves as the rate limiting step in the movement of both xenoestrogen and testosterone through the cell. The greater the bioavailable quantity and greater affinity for the AR loci favors the androgens: Dihydrotestosterone and nandrolone have a 30-fold greater affinity for the AR than 17-β estradiol. While testosterone has a 10-fold greater affinity than 17-β estradiol, 98 percent of testosterone is bound to SHBG. Only 5 percent of nandrolone is bound to SHBG. Nandrolone, milligram for milligram is up to 30 times more important in shifting the FAI toward normalcy. The increased exposure to xenoestrogens and suppression of bioavailable testosterone production favors a state of "Estrogen Dominant".

Estrogen receptor

The discovery of the Estrogen Receptor-α 40 years ago was of interest in those studying breast cancer, endometrial cancer and endometriosis. Estrogen Receptor-β was discovered in 1996 but, the work of Pierdominici [2] and Linares [3] that correlated the loss of the ER-β/ER-α ratio has shifted the focus of medical intervention from chasing inflammatory symptoms with adalimumab in IBD to understanding and now treating causation at the source.

Danazol raises the bioavailable testosterone serum level, measured as the Free Androgen Index, by 2 to 3-fold, primarily by suppressing sex-hormone-binding globulin. As each of the five FDA approved anabolic steroids have unique properties, the various mixtures offer unique treatment opportunities for men and women with advanced Inflammatory Bowel Disease; even those unresponsive to TNF-agonists and those who have underwent exhaustive draconic surgery.

Conclusion

Application of the Scientific Method, the peer reviewed literature and the Case Reports leads Gender Specific Medicine physicians and researchers to four conclusions:

1) Endocrine Disrupting Chemicals (EDCs)/xenoestrogens serve as a *potential cause* that initiates the cascade from health to disease. The biochemical actions of xenoestrogens offer an explanation for the observed estrogenic downreg-

ulation of the Hypothalamic-Pituitary-Gonadal Axis and decreased production of total testosterone.

2) Xenoestrogens stimulate production of sex-hormone-binding globulin which further reduces bioavailable testosterone. The biomarker for the anabolic state of bioavailable testosterone is the Free Androgen Index (FAI). Many disease states have elevated SHBG as biomarker for autoimmune and inflammatory disease [27,28].

3) The relative availability of bioavailable, life-sustaining homeostatic testosterone must affix to the loci in the Androgen Receptor on the cell wall before the hormones enter the cytoplasm and propagate at the Estrogen Receptors on the nucleus. Loss of the bioavailable testosterone allows in more of these "inflammatory estrogen" [2] hormones.

Lastly, once attached to the Estrogen Receptors, the relative ratio of beta/alpha dictates whether the cytoplasm immunological response will be inflammatory or anti-inflammatory. The ER-β/ER-α ratio will be Gender Specific: It is depressed in Crohn's Disease, yet 100-fold increases when inflammation is seen in endometriosis.

The final step of the Scientific Method is the proof of concept. The author has published that the compassionate use of an admixture of anabolic steroids has set the worst case of endometriosis into a 9-year remission, and herein, five of six cases of intractable IBD have experienced 5-year reversal of their disabling state of disease. It is expected that when measurements become available that the ER-β/ER-α in endometriosis will be down-regulated to normal range on appropriate anabolic treatment. It is expected that measurement of the ER-β/ER-α in IBD will be upregulated to a normal range by mixed anabolic therapy. Remission of disease should correlate directly with normalization of both the ER-β/ER-α ratio and the FAI biomarkers as the host's returns to a 'normal' homeostatic range of Gender Specific hormones. The bacterial concept of causation disproved, physicians should ineffective antibiotic therapy and direct treatment to restoring the Free Androgen Index to normal range. A paradigm shift offering compassionate use to our most affected young adults is no longer a hope but a realization.

Summary

The gender specific model of disease

1. Causation of disease: Xenoestrogens in the environment
2. Observation: Downregulation of the normal HPG resulting in lower total testosterone
3. SHBG increased by xenoestrogen. Results: Lower FAI (less TT/more SHBG).
4. Androgen Receptor: Overwhelmed by Estrogen Dominance
5. Increase in Estrogens through AR to Estrogen receptors CREATE INFLAMMATION.

Conflict of Interest

No conflicts of interest.

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