Libido

William M. Kleber DC, D.A.B.C.I

Sponsored by Biotics Research

Order of Todays Presentation

- Libido definition. What is a normal libido?
- Sexy or not sexy; sexual attraction.
- Low or decreased libido: Hypoactive sexual desire disorder (HSDD). Female and Male.
- Sexual Addiction
- Fatigue as a cause of decreased libido
- Hormonal imbalances as a cause of decreased libido: men and women. Hormonal imbalances and treatment.
- Erectile Dysfunction (ED) as a Result of Endothelial Dysfunction
- Testing
- Pharmaceutical meds effect on libido
- Treatment

Libido

- **1**
- **:** instinctual psychic energy that in psychoanalytic theory is derived from primitive biological urges (as for sexual pleasure or self-preservation) and that is expressed in conscious activity
- **2**
- **:** sexual drive

What is Normal Libido?

- Frequency of intercourse?
- Desire. Attraction. Love making?
- Low libido. Physical issue, psychological/social mores.
- Hyper libido vs sex addict

The causes of decreased libido are complex and multifactorial, requiring attention and a careful history to isolate the primary origin. Although dissatisfaction with the relationship or marriage is a common factor in patients with depressed desire, organic causes must also be considered. Physicians must remember that depressed libido is relative and depends on the patient's definition, not on an absolute standard of how frequently people do or should have sexual relations.

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Conditions and Situations Leading to Low Libido

- Relationship issues.
- Medical conditions.
- Hormonal imbalances
- Mental health conditions.
- Certain medications.
- Stress
- Aging

- **How common is low libido?**
- Low libido is common. It affects up to 1 in 5 men and even more women at some point in their lives. It’s also common to experience a drop in sex drive more than once during your life.

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Psychological and social factors that can lead to a decrease in sex drive in anyone include:

- **Relationship problems with your partner**: Relationship issues, such as *problems with communication, trust or intimacy*, are among the most common causes of a decrease in sex drive. A couple's desire for sex also tends to decrease over the course of their relationship.
- **Stress and exhaustion**: Stress, including *stress from work, family or life in general*, can reduce your sex drive by taking your mind off of sexual desire. Chronic stress can also interfere with your hormone levels, resulting in lower libido.
- ***Depression:*** Low self-esteem, feelings of hopelessness and physical fatigue can lower your libido. *Depression also causes an imbalance of the neurotransmitters that help regulate libido*.
- **Anxiety Disorders**: Anxiety can cause increased levels of the hormone cortisol (the "stress hormone"). *High levels of cortisol can suppress the sex hormones that impact your sex drive*.
- **History of sexual trauma**: Experiencing *trauma such as sexual harassment, sexual abuse or rape* can impact your sexual desire.

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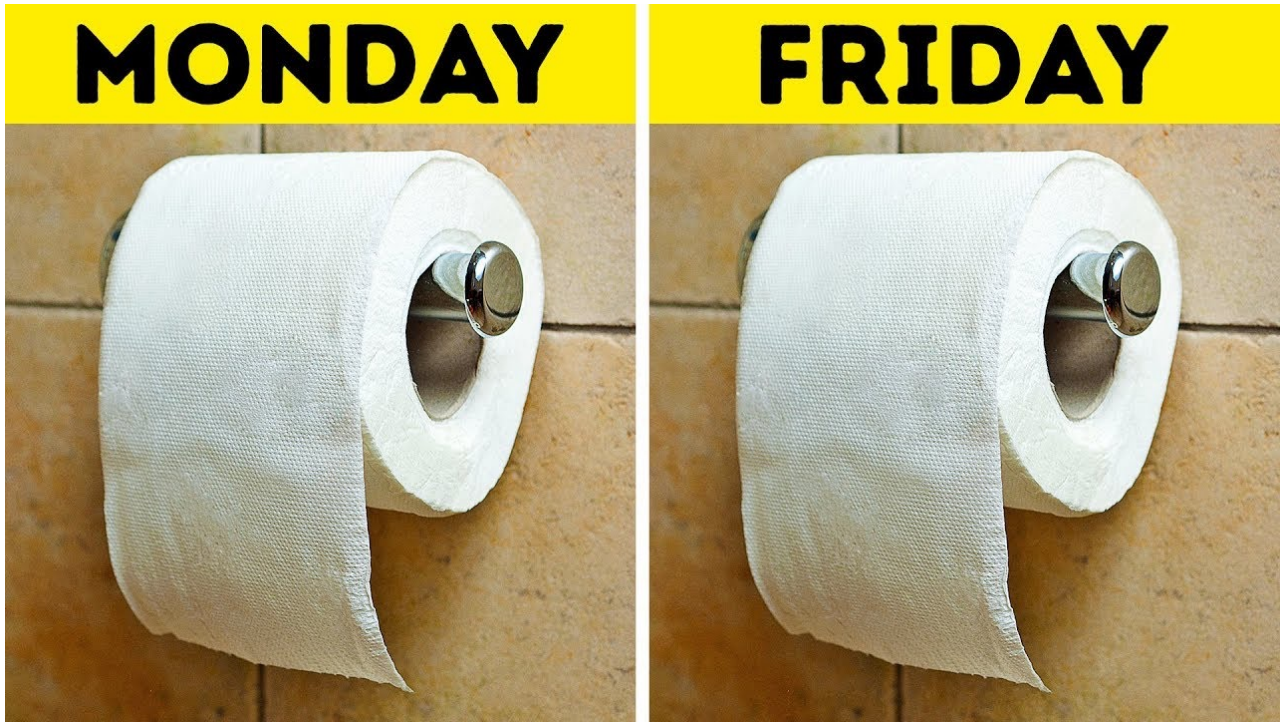
Health Conditions leading to Decreased Sex Drive

- Cancer.
- Chronic kidney disease.
- Chronic pain.
- Diabetes.
- Headaches.
- Heart disease.
- Hyperprolactinemia.
- Hypertension (high blood pressure).
- Hypothyroidism.
- Rheumatoid arthritis.

Sign of Poor Health



Low or decreased libido: **Hypoactive sexual desire disorder (HSDD)**

Hypoactive Sexual Desire Disorder (HSDD)

- Hypoactive sexual desire disorder (HSDD), hyposexuality or inhibited sexual desire (ISD) is sometimes considered a sexual dysfunction, and is characterized as a lack or absence of sexual fantasies and desire for sexual activity, as judged by a clinician.
- For this to be regarded as a disorder, it must cause marked distress or interpersonal difficulties and not be better accounted for by another mental disorder, a drug (legal or illegal), or some other medical condition.

Frellick, Marcia. "FDA Approves New Libido-Boosting Drug for Premenopausal Women". Medscape. WebMD LLC. Retrieved 22 June 2019

HSDD affects approximately 10% of all premenopausal women in the United States, or about 6 million women.

Hypoactive Sexual Desire Disorder (HSDD)

There are various subtypes. HSDD can be **general** (general lack of sexual desire) or **situational** (still has sexual desire but lacks sexual desire for current partner), and it can be **acquired** (HSDD started after a period of normal sexual functioning) or **lifelong** (the person has always had no/low sexual desire).

Decreased Sexual Desire Screener

Please answer each of the following questions by circling either *Yes* or *No*

1. In the past, was your level of sexual desire or interest good and satisfying to you?	***Yes***	***No***
2. Has there been a decrease in your level of sexual desire or interest?	***Yes***	***No***
3. Are you bothered by your decreased level of sexual desire or interest?	***Yes***	***No***
4. Would you like your level of sexual desire or interest to increase?	***Yes***	***No***
5. Please circle all the factors that you feel may be contributing to your current decrease in sexual desire or interest:		
A. An operation, depression, injuries, or other medical condition	***Yes***	***No***
B. Medication, drugs, or alcohol you are currently taking	***Yes***	***No***
C. Pregnancy, recent childbirth, menopausal symptoms	***Yes***	***No***
D. Other sexual issues you may be having (pain, decreased arousal or orgasm)	***Yes***	***No***
E. Your partner's sexual problems	***Yes***	***No***
F. Dissatisfaction with your relationship or partner	***Yes***	***No***
G. Stress or fatigue	***Yes***	***No***

When completed, please give this form back to your clinician.

Clinician:

Verify with the patient each of the answers she has given.

The Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision, characterizes Hypoactive Sexual Desire Disorder (HSDD) as a deficiency or absence of sexual fantasies and desire for sexual activity, which causes marked distress or interpersonal difficulty, and which is not better accounted for by a medical, substance-related, psychiatric, or other sexual condition. HSDD can be either generalized (not limited to certain types of stimulation, situations, or partners) or situational, and can be either acquired (develops only after a period of normal functioning) or lifelong.

If the patient answers "YES" to all of the questions 1 through 4, and your review confirms "NO" to all of the factors in question 5, then she qualifies for the diagnosis of generalized acquired HSDD.

If the patient answers "YES" to all of the questions 1 through 4 and "YES" to any of the factors in question 5, then decide if the answers to question 5 indicate a primary diagnosis other than generalized acquired HSDD. Co-morbid conditions such as arousal or orgasmic disorder do not rule out a concurrent diagnosis of HSDD.

If the patient answers "NO" to any of the questions 1 through 4, then she does not qualify for the diagnosis of generalized acquired HSDD.

Boehringer Ingelheim International

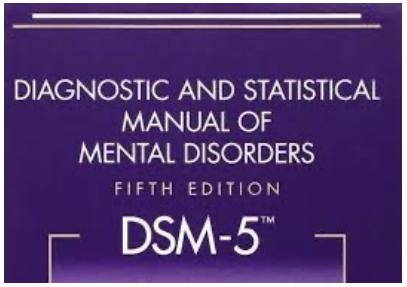
Hypoactive Sexual Desire Disorder (HSDD)

- ICD-10 code **F52. 0** for Hypoactive sexual desire disorder is a medical classification as listed by WHO under the range - Mental, Behavioral and Neurodevelopmental disorders .

- It was first included in the DSM-III under the name inhibited sexual desire disorder, but the name was changed in the DSM-III-R. Other terms used to describe the phenomenon include sexual aversion and sexual apathy. More informal or colloquial terms
are frigidity and frigidness.

Hypoactive Sexual Desire Disorder (HSDD)

Low sexual desire alone is not equivalent to HSDD because of the requirement in HSDD *that the low sexual desire causes marked distress and interpersonal difficulty* and because of the requirement that the low desire is not better accounted for by another disorder in the DSM or by a general medical problem. It is therefore difficult to say exactly what causes HSDD. It is easier to describe, instead, some of the causes of low sexual desire.



Female Sexual Interest/Arousal Disorder

American Psychiatric Association, ed. (2013)., 302.72 (F52.22)". *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*. American Psychiatric Publishing.

pp. 433–437.

Female sexual interest/arousal disorder is defined as a "lack of, or significantly reduced, sexual interest/arousal", manifesting as at least three of the following symptoms: no or little interest in sexual activity, no or few sexual thoughts, no or few attempts to initiate sexual activity or respond to partner's initiation, no or little sexual pleasure/excitement in 75–100% of sexual experiences, no or little sexual interest in internal or external erotic stimuli, and no or few genital/nongenital sensations in 75–100% of sexual experiences.

Prevalence of low sexual desire and hypoactive sexual desire disorder in a nationally representative sample of US women

Arch Intern Med
. 2008 Jul 14;168(13):1441-9.
doi: 10.1001/archinte.168.13.1441

Suzanne L West [1], Aimee A D'Aloisio, Robert P Agans, William D Kalsbeek, Natalie N Borisov, John M Thorp

- **Abstract**
- **Background:** We sought to estimate the prevalence of low sexual desire and hypoactive sexual desire disorder (HSDD) in US women, focusing on their menopausal status.
- **Results:** Prevalence of low sexual desire ranged from 26.7% among premenopausal women to 52.4% among naturally menopausal women. The prevalence of HSDD was highest among surgically menopausal women (12.5%).
- **Conclusions: Prevalence of low sexual desire is elevated among surgically and naturally menopausal women vs premenopausal women.** Distress about low desire (HSDD) appears to be more than twice as prevalent among surgically menopausal women vs premenopausal women, although the estimate is fairly imprecise.

archives of sexual behavior
An Interdisciplinary Research Journal

"Attentional and Affective Processing of Sexual Stimuli in Women with Hypoactive Sexual Desire Disorder".

Brauer M, van leeuwen M, Janssen E, Newhouse SK, Heiman JR, Laan E (September 2011). *Archives of Sexual Behavior*. **41** (4): 891–905.

Additionally, factors such as relationship problems or stress are believed to be possible causes of reduced sexual desire in women. According to one recent study examining the affective responses and attentional capture of sexual stimuli in women with and without HSDD, women with HSDD do not appear to have a negative association to sexual stimuli, but rather a weaker positive association than women without HSDD.

2005 Mar-Apr;17(2):148-53.
doi: 10.1038/sj.ijir.3901294.

Women with low libido: correlation of decreased androgen levels with female sexual function index

B Turna [1], E Apaydin, B Semerci, B Altay, N Cikili, O Nazli

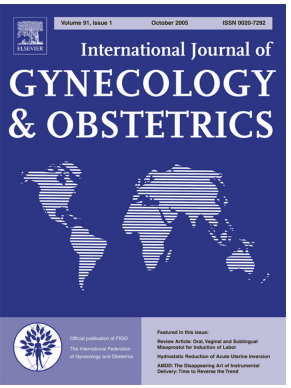
- The aim of the present study was to investigate a possible correlation between decreased androgen levels and female sexual function index (FSFI) in women with low libido and compare these findings with normal age-matched subjects. In total, 20 premenopausal women with low libido (mean age 36.7; range 24-51 y) and 20 postmenopausal women with low libido (mean age 54; 45-70 y), and 20 premenopausal healthy women (mean age 32.2; range 21-51 y) and 20 postmenopausal healthy women (mean age 53.5; range 48-60 y) as controls were enrolled in the current study. Women with low libido had symptoms for at least 6 months and were in stable relationships. All premenopausal patients had regular menstrual cycles and all postmenopausal patients and controls were on estrogen replacement therapy. None of the patients were taking birth control pills, corticosteroids or had a history of chronic medical illnesses. All completed the FSFI and Beck's Depression Inventory (BDI) questionnaires. Hormones measured included: cortisol; T3, T4 and TSH; estradiol; total and free testosterone; dehydroepiandrosterone sulfate (DHEA-S); sex hormone binding globulin (SHBG).
- We performed statistical analysis by parametric and nonparametric comparisons and correlations, as appropriate. We found significant differences between the women with low libido and the controls in total testosterone, free testosterone and DHEA-S levels and full-scale FSFI score for both pre- and postmenopausal women ($P<0.05$). In addition, decreased total testosterone, free testosterone and DHEA-S levels positively correlated with full-scale FSFI score and FSFI-desire, FSFI-arousal, FSFI-lubrication and FSFI-orgasm scores ($P<0.05$). Our data suggest that women with low libido have lower androgen levels compared to age-matched normal control groups and their decreased androgen levels correlate positively with female sexual function index domains.

Our data suggest that women with low libido have lower androgen levels compared to age-matched normal control groups

Androgen therapy in women: a reappraisal: an endocrine society clinical practice guideline

Wierman, ME; Arlt, W; Basson, R; et al. (Oct 2014). "Androgen therapy in women: a reappraisal: an endocrine society clinical practice guideline". *The Journal of Clinical Endocrinology and Metabolism*. **99** (10): 3489–510. doi:10.1210/jc.2014-2260. PMID 25279570.

Testosterone supplementation is effective in the short term. However, its long-term safety is unclear.



The pathophysiology of hypoactive sexual desire disorder in women

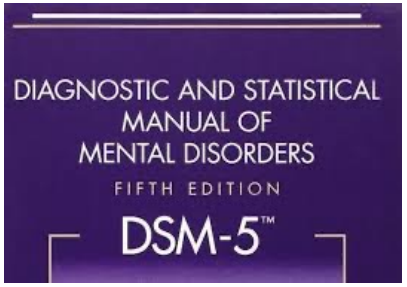
Clayton AH (July 2010). ". *Int J Gynaecol Obstet*. **110** (1): 7–11. doi:10.1016/j.ijgo.2010.02.014. PMID 20434725. S2CID 29172936

One theory suggests that sexual desire is controlled by a balance between inhibitory and excitatory factors. This is thought to be expressed via neurotransmitters in selective brain areas. A decrease in sexual desire may therefore be due to an imbalance between neurotransmitters with excitatory activity like dopamine and norepinephrine and neurotransmitters with inhibitory activity, like serotonin.

addyi (flibanserin)

ADDYI IS THE #1 PRESCRIBED TREATMENT FOR HSDD

addyi is a non-hormonal, multifunctional serotonin agonist antagonist (MSAA). Addyi appears to corrects an imbalance of the neurotransmitters (brain chemicals) dopamine and norepinephrine (both responsible for sexual excitement), while decreasing levels of serotonin (which can lower sex drive)



Male Hypoactive Sexual Desire Disorder

American Psychiatric Association, ed. (2013). "Male Hypoactive Sexual Desire Disorder, 302.71 (F52.0)". *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*. American Psychiatric Publishing. pp. 440–443.

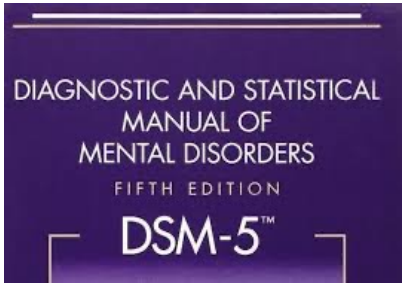
In the DSM-5, male hypoactive sexual desire disorder is characterized by "persistently or recurrently deficient (or absent) sexual/erotic thoughts or fantasies and desire for sexual activity", as judged by a clinician with consideration for the patient's age and cultural context

Hypoactive Sexual Desire Disorder (HSDD) in Men

- In men, though there are theoretically more types of HSDD/low sexual desire, typically men are only diagnosed with one of three subtypes.
- **Lifelong/generalized:** The man has little or no desire for sexual stimulation (with a partner or alone) and never had.
- **Acquired/generalized:** The man previously had sexual interest in his present partner, but lacks interest in sexual activity, partnered or solitary.
- **Acquired/situational:** The man was previously sexually interested in his present partner but now lacks sexual interest in this partner but has desire for sexual stimulation (i.e. alone or with someone other than his present partner.)

Hypoactive Sexual Desire Disorder (HSDD) in Men

- Though it can sometimes be difficult to distinguish between these types, they do not necessarily have the same cause. The *cause of **lifelong/generalized HSDD** is unknown*. In the case of **acquired/generalized low sexual desire**, possible causes include various medical/health problems, psychiatric problems, low levels of testosterone or high levels of prolactin.
- Too much prolactin reduces the levels of both estrogen and progesterone. Too much prolactin also can prevent the release of an egg during the menstrual cycle (anovulation) in females. *In males, too much prolactin also can lead to decreased sperm production*. Bone loss (osteoporosis).



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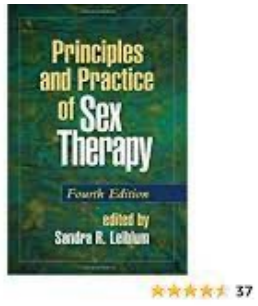
American Psychiatric Association, ed. (2013). "Male Hypoactive Sexual Desire Disorder, 302.71 (F52.0)". *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*. American Psychiatric Publishing. pp. 440–443.

For both diagnoses, symptoms must persist for at least six months, cause clinically significant distress, and not be better explained by another condition. Simply having lower desire than one's partner is not sufficient for a diagnosis. Self-identification of a lifelong lack of sexual desire as asexuality precludes diagnosis.



"Sexual Desire Disorders in Men"

Maurice, William (2007). In Leiblum, Sandra (ed.). *Principles and Practice of Sex Therapy* (4th ed.). New York: The Guilford Press.

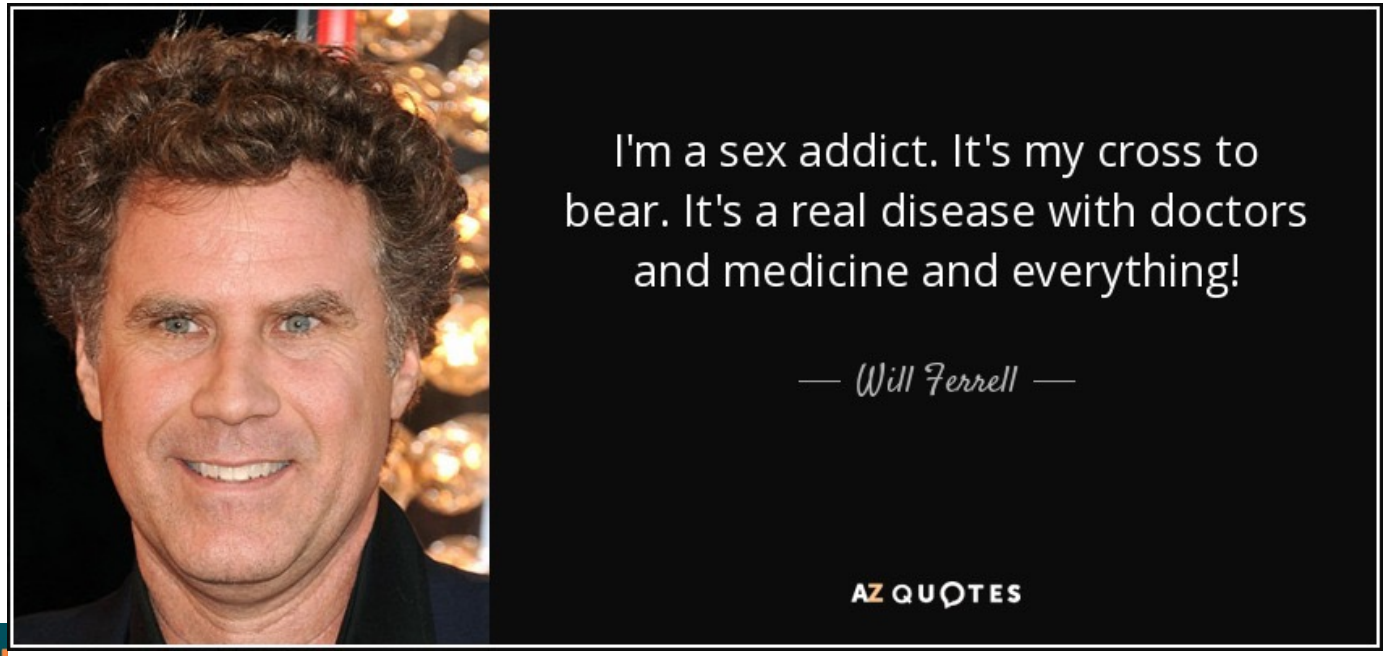
Low sexual desire can also be a side effect of various medications. In the case of acquired/situational HSDD, possible causes include intimacy difficulty, relationship problems, sexual addiction, and chronic illness of the man's partner. The evidence for these is somewhat in question. Some claimed causes of low sexual desire are based on empirical evidence. However, some are based merely on clinical observation.

Childs, Dan (January 15, 2009). "Asexuals Push for Greater Recognition". *abcnews.go.com*. ABC News. Retrieved January 11, 2022.

HSDD may function to pathologize asexuals, though their lack of sexual desire may not be maladaptive. Because of this, some members of the asexual community lobbied the mental health community working on the DSM-5 to regard asexuality as a legitimate sexual orientation rather than a mental disorder.

Normal Libido

Somewhere between no desire for sex and sexual addiction



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Who Is a Sex Addict?

By ROBERT WEISS, LCSW, CSAT-S

Increasing numbers of men and women are seeking clinical treatment for sexual addiction. This is partly the result of the increasingly endless variety of Internet-based sexual content, and partly the result of easy accessibility of anonymous sexual partnering via smartphone apps and social media.

It is estimated that three to six percent of the general U.S. population suffers from some form of addictive sexual behavior with self or others. However, the current lack of a universally recognizable clinical diagnosis — combined with a dearth of publicly funded research and ongoing cultural shame and stigma regarding sexual disorders in general — likely prevent many more individuals from identifying the problem and seeking help.

Traditionally, the majority of inpatient and outpatient sexual addiction patients (approximately 85 percent) have been adult males. However, there is growing awareness that women also struggle with the disorder and they, too, are seeking help in increasing numbers.

Typical Sex Addict Behaviors

Below is a brief overview of common behaviors exhibited by active sexual addicts:

- Compulsive masturbation with or without pornography
- Ongoing abuse of soft- and hard-core porn
- Multiple affairs and brief "serial" relationships
- Attending strip clubs, adult bookstores and similar sex-focused environments

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Spokeo.com/Cheating-Spouse-Search

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HaveTheRelationshipYouWant.com

DSM-5 Proposed criteria for hypersexual disorder

A. Over a period of at least six months, recurrent and intense sexual fantasies, sexual urges, and sexual behavior in association with four or more of the following five criteria:
   1. Excessive time is consumed by sexual fantasies and urges, and by planning for and engaging in sexual behavior.
   2. Repetitively engaging in these sexual fantasies, urges, and behavior in response to dysphoric mood states (e.g., anxiety, depression, boredom, irritability).
   3. Repetitively engaging in sexual fantasies, urges, and behavior in response to stressful life events.
   4. Repetitive but unsuccessful efforts to control or significantly reduce these sexual fantasies, urges, and behavior.
   5. Repetitively engaging in sexual behavior while disregarding the risk for physical or emotional harm to self or others.

B. There is clinically significant personal distress or impairment in social, occupational or other important areas of functioning associated with the frequency and intensity of these sexual fantasies, urges, and behavior.

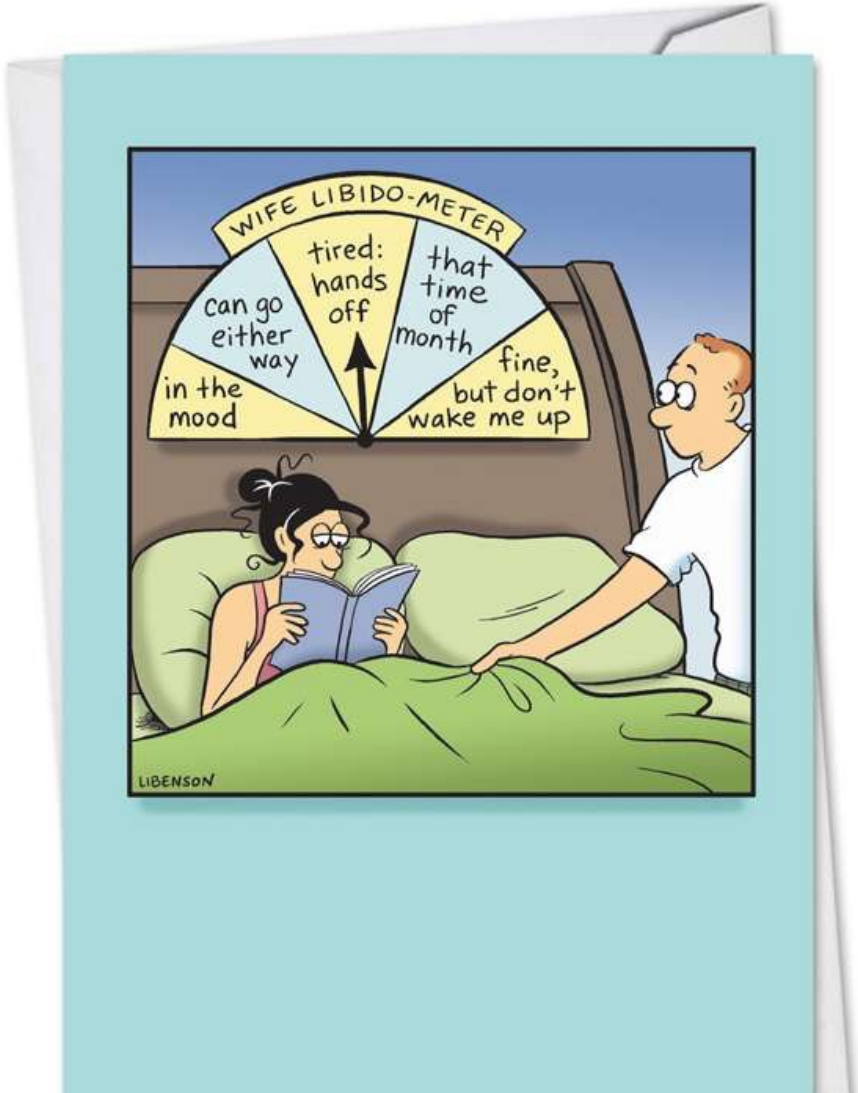
C. These sexual fantasies, urges, and behavior are not due to direct physiological effects of exogenous substances (e.g., drugs of abuse or medications), a co-occurring general medical condition, or to manic episodes.

D. The person is at least 18 years of age.

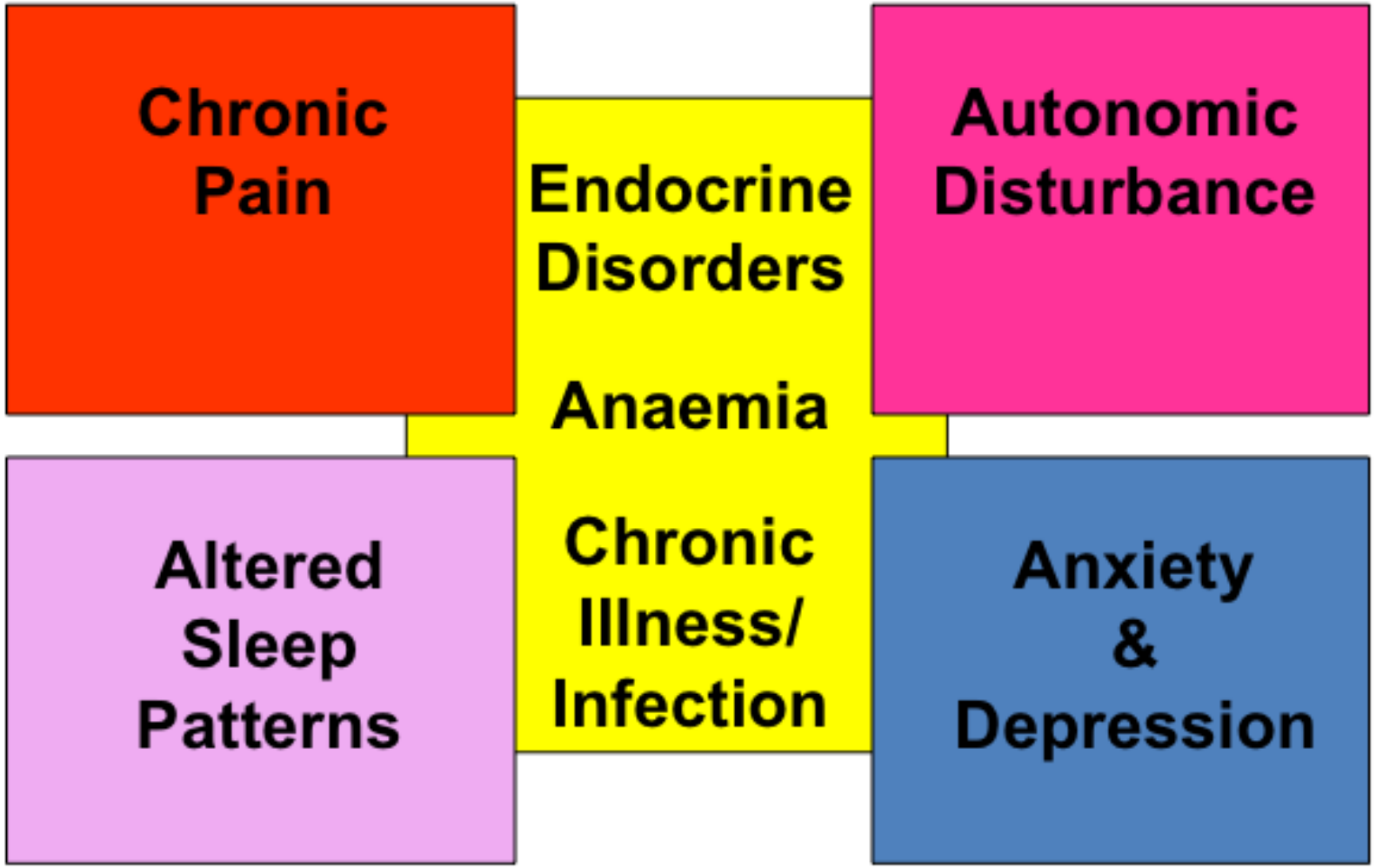
Specify if: Masturbation, Pornography, Sexual Behavior With Consenting Adults, Cybersex, Telephone Sex, Strip Clubs

Fatigue as a cause of decreased libido

Fatigue and Decreased Libido



Chronic Fatigue



Fatigue

- Fatigue is the symptom that arises when energy demands exceed energy delivery.
- Our basic physiological function such as heart, gut, brain, kidney and liver function consume about 2/3 of our energy each day. The other 1/3 is for our physical actions and mental function.
- Either our fatigued patients are not making enough energy or we are spending too much energy or a little bit of both.
- Common areas of excessive energy spending are the emotional and immunological areas. Example is the flu.

Fatigue

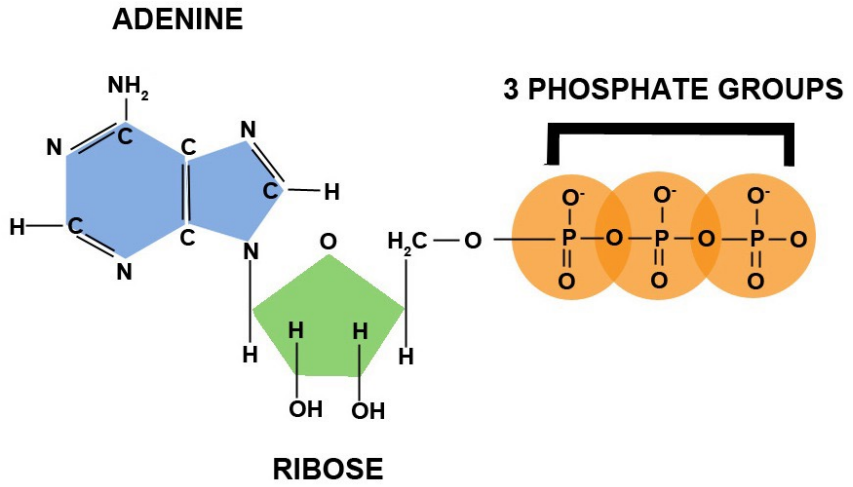
- Many cases of chronic fatigue follow acute infection either viral or bacterial.
- Symptoms of Chronic Fatigue result from poor energy production at the cellular level. Energy availability is partially determined by mitochondrial function.
- Depression may be part of CFS because for neurotransmitters like serotonin and acetylcholine to be effective, they require ATP.
- There are genetic predispositions to CFS but these genetic tendencies need to be turned on or off by environmental influences.

Fatigue

- Environmental influences can include:
- Damage to DNA
- Toxins
- Damage from free radicals
- Hormone imbalances
- Poor energy supply (diet)
- Inflammation

Energy is a Molecule

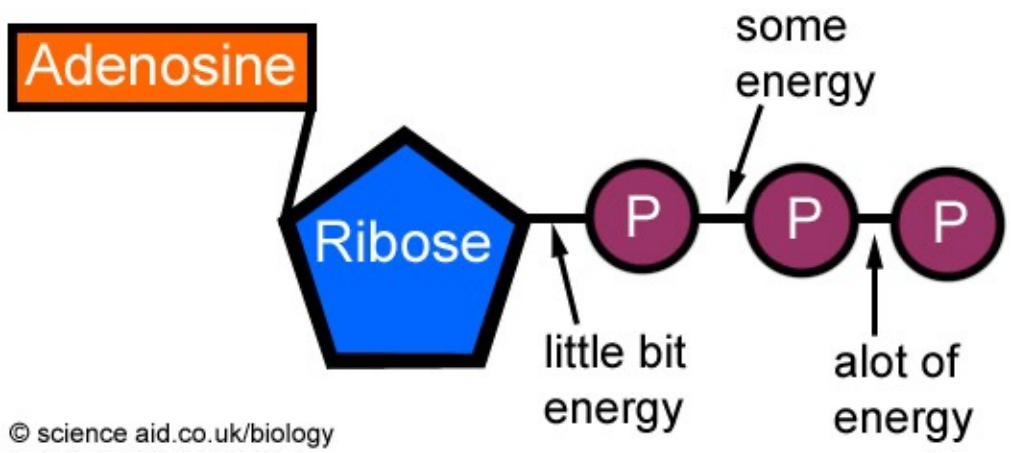
Adenosine Triphosphate



"Just as commerce is facilitated by the use of a common currency, the commerce of the cell—metabolism—is facilitated by the use of a common energy currency, *adenosine triphosphate* (ATP)."- Biochemistry 5th edition

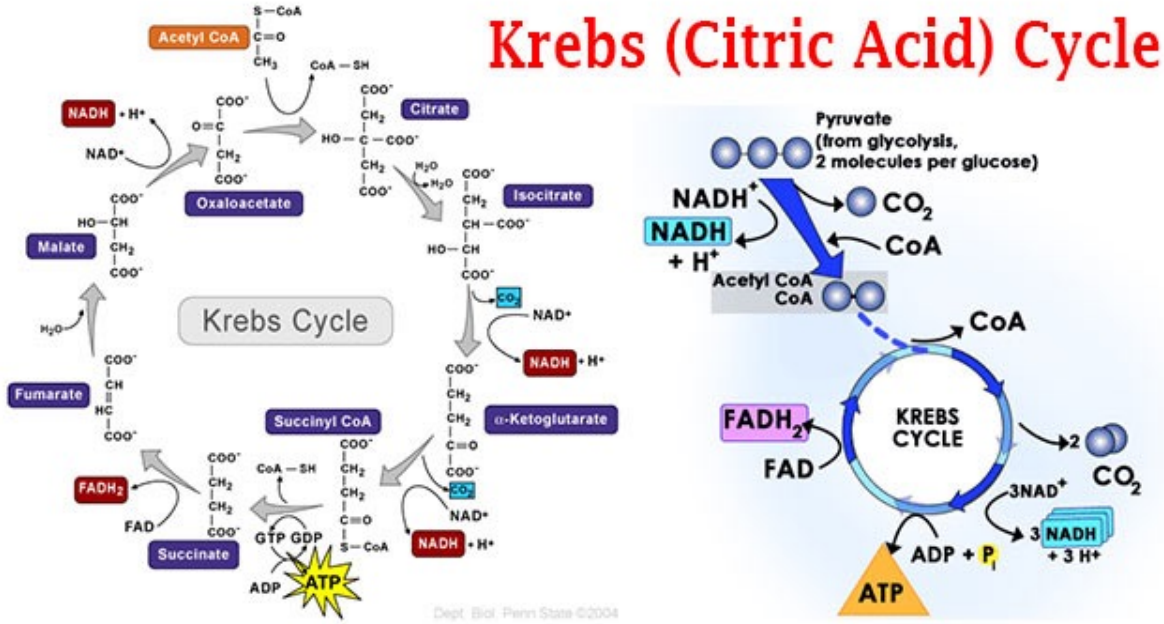
Energy Production at the Cellular Level

The job of the mitochondria is to provide energy in the form of a chemical compound called adenosine triphosphate (ATP) .

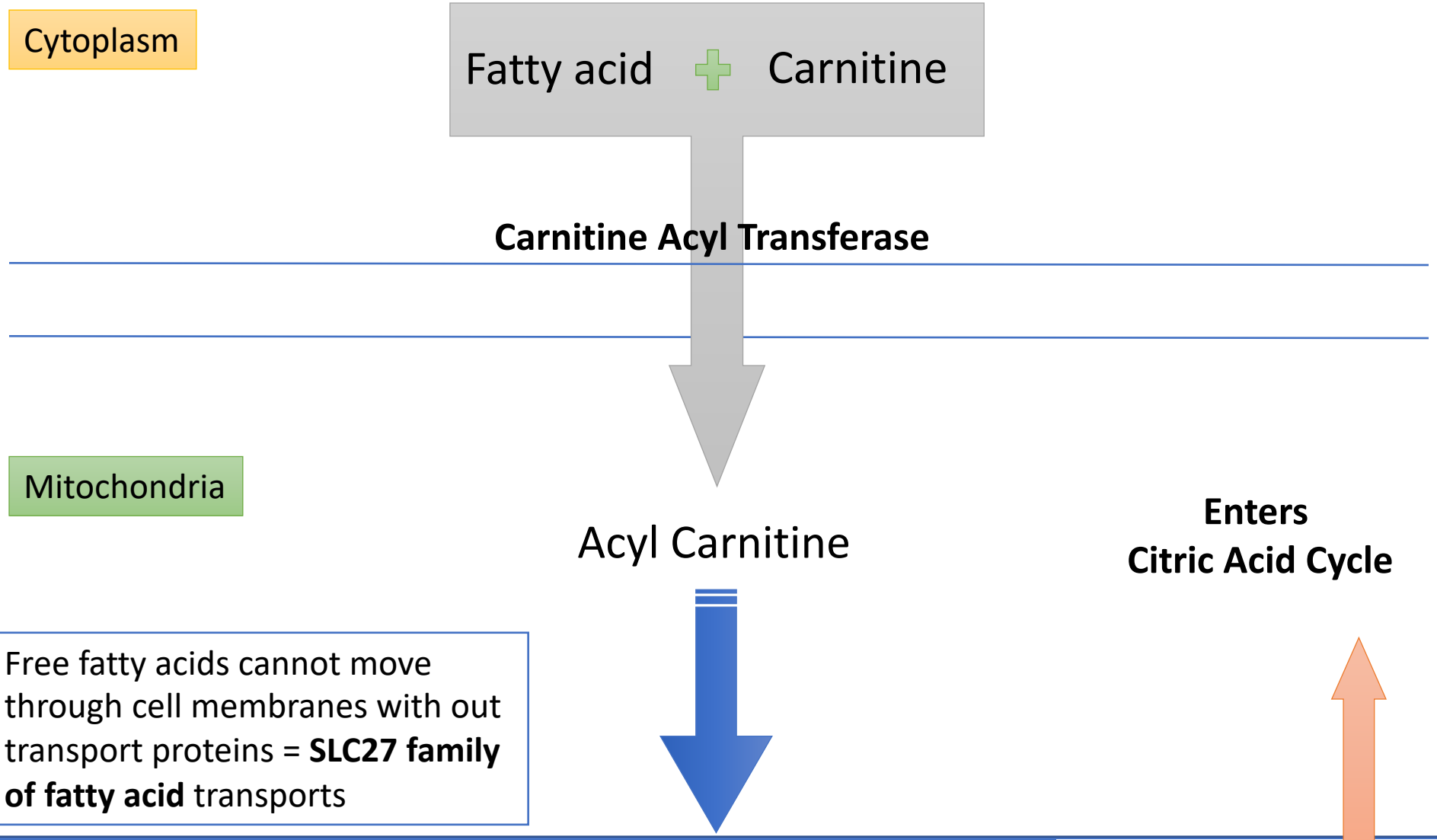


Energy Production at the Cellular Level

Protein, fats and carbohydrates are digested and absorbed in the gut. Much of this is turned into glucose. Glucose is largely stored in the liver. Glucose enters cells and is converted into a form of acetate called pyruvate. This is shunted into the mitochondria by acetyl L carnitine. Acetate, as pyruvate then enters process called the citric acid cycle or Krebs cycle.



Fatty Acid Metabolism-Beta Oxidation



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Energy Production at the Cellular Level

- ATP (adenosine with three phosphate groups) is converted to ADP (adenosine with 2 phosphate groups) with the release of energy for work. ADP then passes back into the mitochondria with the help of the tranlocator proteins where it is recycled back to ATP through a process called oxidative phosphorylation.
- In a healthy person, ATP recycles every 10 seconds.

Fatty Acid Oxidation

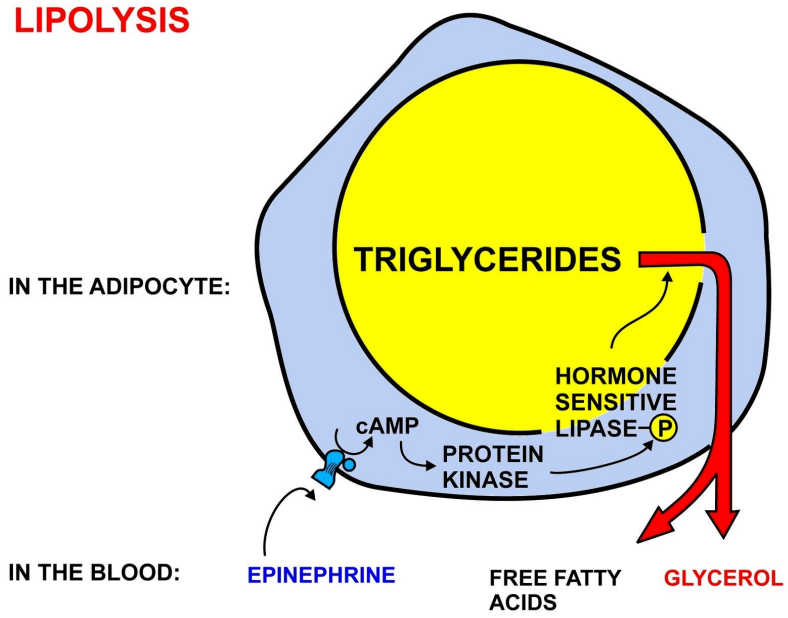
- Utilization of dietary lipids requires that they first be absorbed through the intestines. Lipids are insoluble in the aqueous intestinal environment.
- Emulsification of lipids is accomplished through agitation in the stomach and through the action of bile salts that are formed in the liver and secreted by the gall bladder.

Fatty Acid Oxidation

- Dietary lipids in the form of triglycerides and phospholipids are broken down by lipases secreted at various parts of the digestive tract.
- The primary source of fatty acids for oxidation are dietary. They are transported through the blood as chylomicrons. Stored in adipose tissue. Fatty acids are liberated through adipose triglyceride lipase (ATGL).

Fatty Acid Oxidation

- Epinephrine, norepinephrine and glucagon stimulate fatty acid release from adipose cells.
- Then fatty acids are released from adipose tissue stores, they are released as free fatty acids and are bound to protein such as albumin as transport proteins.



Mitochondrial Beta Oxidation

- Oxidation of fatty acids occurs in mitochondria and peroxisomes.
- Fatty acids of between 4-8 and between 6-12 carbon atoms in length are referred to as short and medium chain fatty acids. Long chain fatty acids ,10-16 carbons long , are oxidized in the mitochondria and peroxisomes with the peroxisomes having preference for those over 14 carbons atoms long.

MCT- Medium Chain Triglycerides

PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Medium-Chain Triglyceride Feeding in Premature Infants: Effects on Fat and Nitrogen Absorption

Phienvit Tantibhedhyangkul and Sami A Hashim

Pediatrics 1975;55;359

The online version of this article, along with updated information and services, is located on the World Wide Web at:
/content/55/3/359

When 40% of the total fat calories of the formula was derived from MCT, the percentage of fat absorption of the premature infants was improved to the level found in normal full-term infants.

When 80% of the total fat calories of the formula were contributed by MCT, the percentage of fat absorption of the premature infant was **improved to the level found in adults.** Virtually *all* of the medium-chain fatty acids in both MCT formulas fed during both periods were absorbed.

The results clearly demonstrate that MCT feeding is feasible in premature infants and medicate that such infants absorb MCT more efficiently than LCT.

Mitochondrial Beta Oxidation

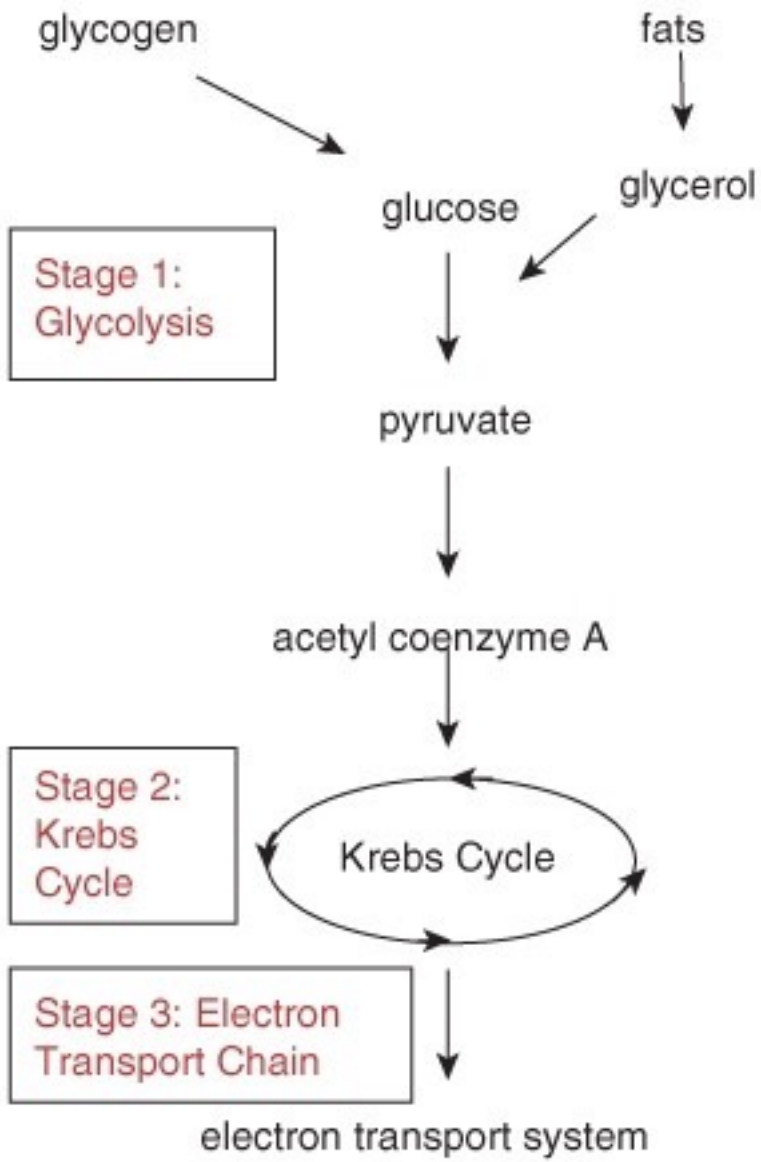
- The transport of acyl-CoA into the mitochondria is accomplished via acyl-carnitine.
- The process of mitochondrial fatty acid oxidation is termed beta oxidation since it occurs through the sequential removal of 2 carbon units at the beta carbon position of the fatty acyl- CoA molecule.

Glycolysis

- **Glycolysis** (from *glycose*, an older term for glucose + -*lysis* degradation) is the metabolic pathway that converts glucose $C_6H_{12}O_6$, into pyruvate, $CH_3COCOO^- + H^+$. The free energy released in this process is used to form the high-energy compounds ATP (adenosine triphosphate) and NADH (reduced nicotinamide adenine dinucleotide)

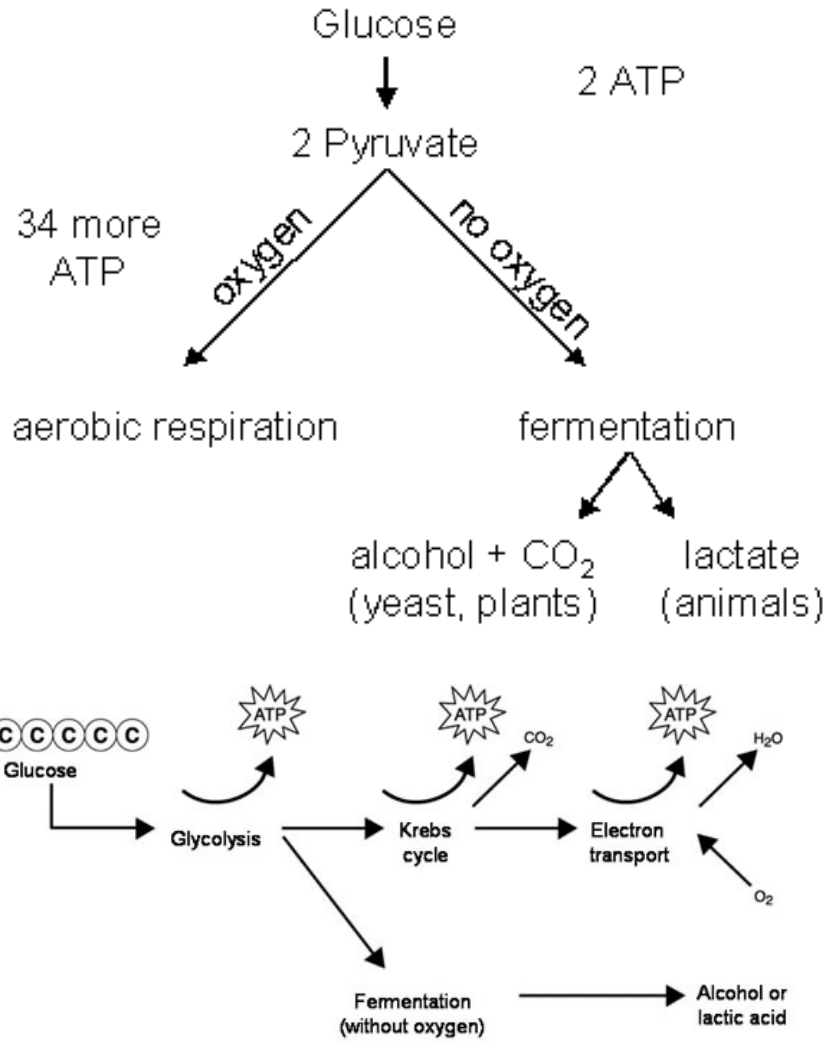
Glycolysis

- **Pyruvic acid** ($CH_3COCOOH$) is the simplest of the alpha-keto acids.
- Pyruvic acid can be made from glucose through glycolysis, converted back to carbohydrates (such as glucose) via gluconeogenesis, or to fatty acids through a reaction with acetyl-CoA.

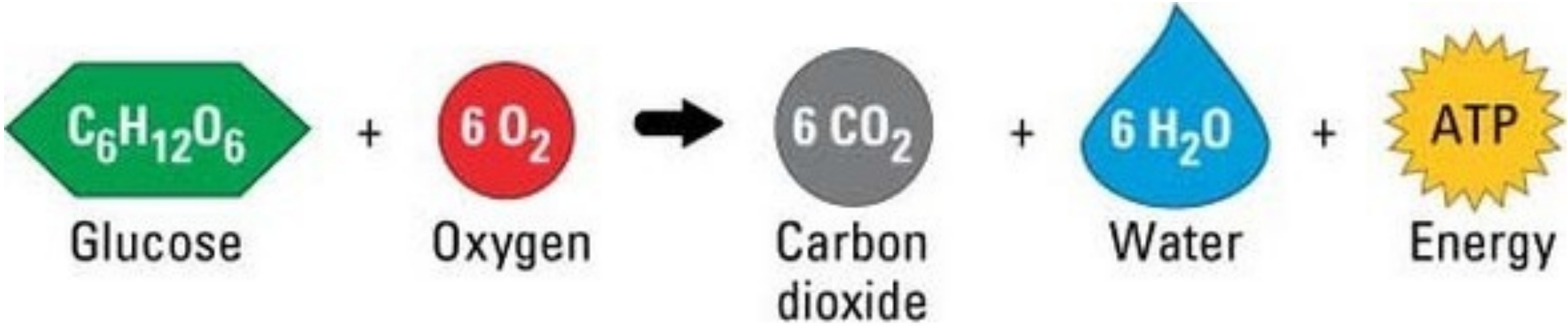


Glycolysis

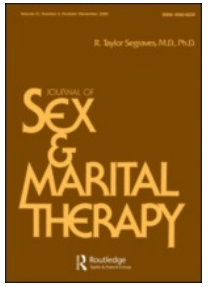
- Pyruvic acid supplies energy to cells through the citric acid cycle (also known as the Krebs cycle) when oxygen is present (aerobic respiration), and alternatively ferments to produce lactate when oxygen is lacking (fermentation)



End Products of Glycolysis : Aerobic Respiration



J Sex Marital Ther
. 2008;34(3):240-7.
doi: 10.1080/00926230701866232.



Sexual dysfunction as related to severity of fatigue in women with CFS

A Blazquez[1], E Ruiz, A Vazquez, T Fernandez de Sevilla, A Garcia-Quintana, J Garcia-Quintana, J Alegre

- **Abstract**
- To assess sexual function in women with chronic fatigue syndrome. The study included 27 women, aged 20 to 45 years, with chronic fatigue syndrome (CFS) and 15 healthy female controls. Sexual function was measured with the Golombok Rust Inventory of Sexual Satisfaction (GRISS) questionnaire and five clinical questions. In the patient group, total fatigue impact scale (FIS) score correlated with the GRISS satisfaction (r:-0.471, P < .005), avoidance (r: 0.632, P < .001) and sensuality (r: -0.445, P = .008) subscales. **The GRISS satisfaction, avoidance, and sensuality subscale results and the fact of seeing the sexual act as a negative experience correlated with the intensity of fatigue in women with CFS.**

1a) Some women experience lack of or low sexual interest/desire in sex. Has this happened to you during the last 6 months? 0. Never/almost never 1. Rarely 2. Sometimes 3. Often 4. Almost all the time/Always	1b) Has this been a personal problem for you? 0. Not at all a problem 1. A very small problem 2. Some problem 3. A considerable problem 4. A very great problem
2a) Some women do not experience physical sexual excitement (e.g., genital swelling, vaginal wetness, tingling sensation) during sexual stimulation and/or sexual activity. Has this happened to you during the last 6 months? O No sexual activity 0. Never/almost never 1. Rarely 2. Sometimes 3. Often 4. Almost all the time/Always	2b) Has this been a personal problem for you? 0. Not at all a problem 1. A very small problem 2. Some problem 3. A considerable problem 4. A very great problem
3a) Some women do not feel sexually turned on or do not have pleasurable sexual feelings when engaging in sexual activity. Has this happened to you during the last 6 months? O No sexual activity 0. Never/almost never 1. Rarely 2. Sometimes 3. Often 4. Almost all the time/Always	3b) Has this been a personal problem for you? 0. Not at all a problem 1. A very small problem 2. Some problem 3. A considerable problem 4. A very great problem
4a) Some women experience difficulties reaching orgasm during sexual activities despite feeling sexually excited. Has this happened to you during the last 6 months? O No sexual activity 0. Never/almost never 1. Rarely 2. Sometimes 3. Often 4. Almost all the time/Always	4b) Has this been a personal problem for you? 0. Not at all a problem 1. A very small problem 2. Some problem 3. A considerable problem 4. A very great problem
5a) Some women experience genital pain during or shortly after sexual activity. Has this happened to you during the last 6 months? O No sexual activity 0. Never/almost never 1. Rarely 2. Sometimes 3. Often 4. Almost all the time/Always	5b) Has this been a personal problem for you? 0. Not at all a problem 1. A very small problem 2. Some problem 3. A considerable problem 4. A very great problem
6a) Some women experience difficulties allowing vaginal penetration despite their wish to do so. Has this happened to you during the last 6 months? O No sexual activity 0. Never/almost never 1. Rarely 2. Sometimes 3. Often 4. Almost all the time/Always	6b) Has this been a personal problem for you? 0. Not at all a problem 1. A very small problem 2. Some problem 3. A considerable problem 4. A very great problem
7a) Some women experience persistent and unwanted genital arousal (tingling, throbbing, pulsating) in the absence of any sexual interest. Has this happened to you during the last 6 months? 0. Never/almost never 1. Rarely 2. Sometimes 3. Often 4. Almost all the time/Always	7b) Has this been a personal problem for you? 0. Not at all a problem 1. A very small problem 2. Some problem 3. A considerable problem 4. A very great problem
8a) During the last 6 months, my sexual life has been: 0. Very unsatisfying 1. Unsatisfying 2. Rather unsatisfying 3. Rather satisfying 4. Satisfying 5. Very satisfying	
10) Is there anything else you would like to tell us with respect to your sexual life? For those who have not been sexually active during the last 6 months please explain why you have been sexually inactive.	
11) Would you want your physician (counselor) to further explore sexual difficulties and/or problems with you?	0. No 1. Not now 2. Yes

Infections and Fatigue

- Energy can be under produced, or we can spend excessive amounts on upregulated physiological functions.
- Fighting infection takes ATP.

- Epstein Barr Virus
- Mycoplasma
- Strep infections
- Prostatitis,
- Gingivitis
- Intestinal dysbiosis
- Interstitial cystitis
- Sinusitis
- Tonsillitis
- Dermatitis
- Vaginitis
- Yeast infection
- Parasites

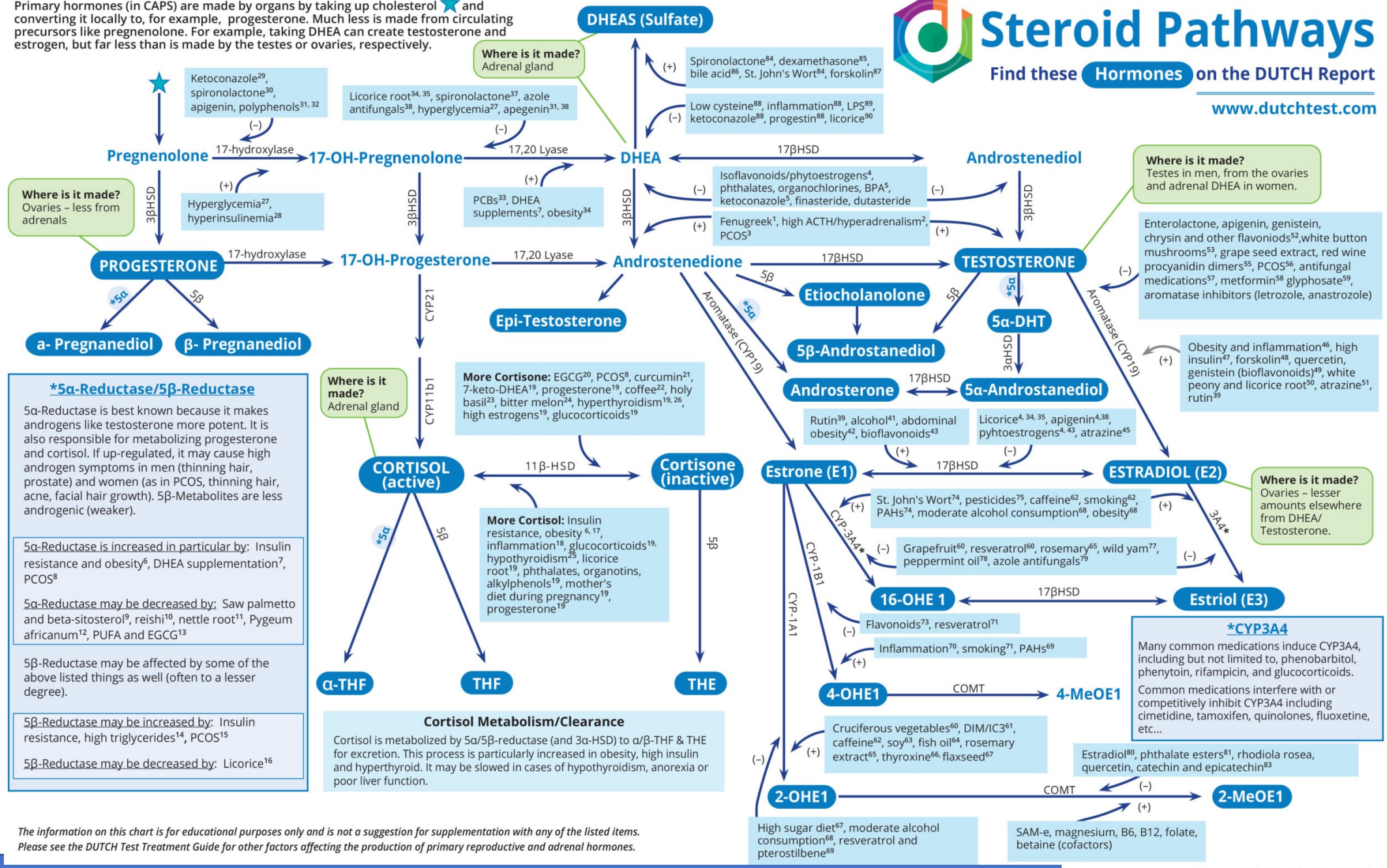
Hormonal imbalances as a cause of decreased libido: men and women.

Steroid Pathways

Find these **Hormones** on the DUTCH Report

www.dutchtest.com

Primary hormones (in CAPS) are made by organs by taking up cholesterol ★ and converting it locally to, for example, progesterone. Much less is made from circulating precursors like pregnenolone. For example, taking DHEA can create testosterone and estrogen, but far less than is made by the testes or ovaries, respectively.



*5α-Reductase/5β-Reductase

5α-Reductase is best known because it makes androgens like testosterone more potent. It is also responsible for metabolizing progesterone and cortisol. If up-regulated, it may cause high androgen symptoms in men (thinning hair, prostate) and women (as in PCOS, thinning hair, acne, facial hair growth). 5β-Metabolites are less androgenic (weaker).

5α-Reductase is increased in particular by: Insulin resistance and obesity[6], DHEA supplementation[7], PCOS[8]

5α-Reductase may be decreased by: Saw palmetto and beta-sitosterol[9], reishi[10], nettle root[11], Pygeum africanum[12], PUFA and EGCG[13]

5β-Reductase may be affected by some of the above listed things as well (often to a lesser degree).

5β-Reductase may be increased by: Insulin resistance, high triglycerides[14], PCOS[15]

5β-Reductase may be decreased by: Licorice[16]

Cortisol Metabolism/Clearance

Cortisol is metabolized by 5α/5β-reductase (and 3α-HSD) to α/β-THF & THE for excretion. This process is particularly increased in obesity, high insulin and hyperthyroid. It may be slowed in cases of hypothyroidism, anorexia or poor liver function.

*CYP3A4

Many common medications induce CYP3A4, including but not limited to, phenobarbitol, phenytoin, rifampicin, and glucocorticoids.

Common medications interfere with or competitively inhibit CYP3A4 including cimetidine, tamoxifen, quinolones, fluoxetine, etc...

The information on this chart is for educational purposes only and is not a suggestion for supplementation with any of the listed items. Please see the DUTCH Test Treatment Guide for other factors affecting the production of primary reproductive and adrenal hormones.

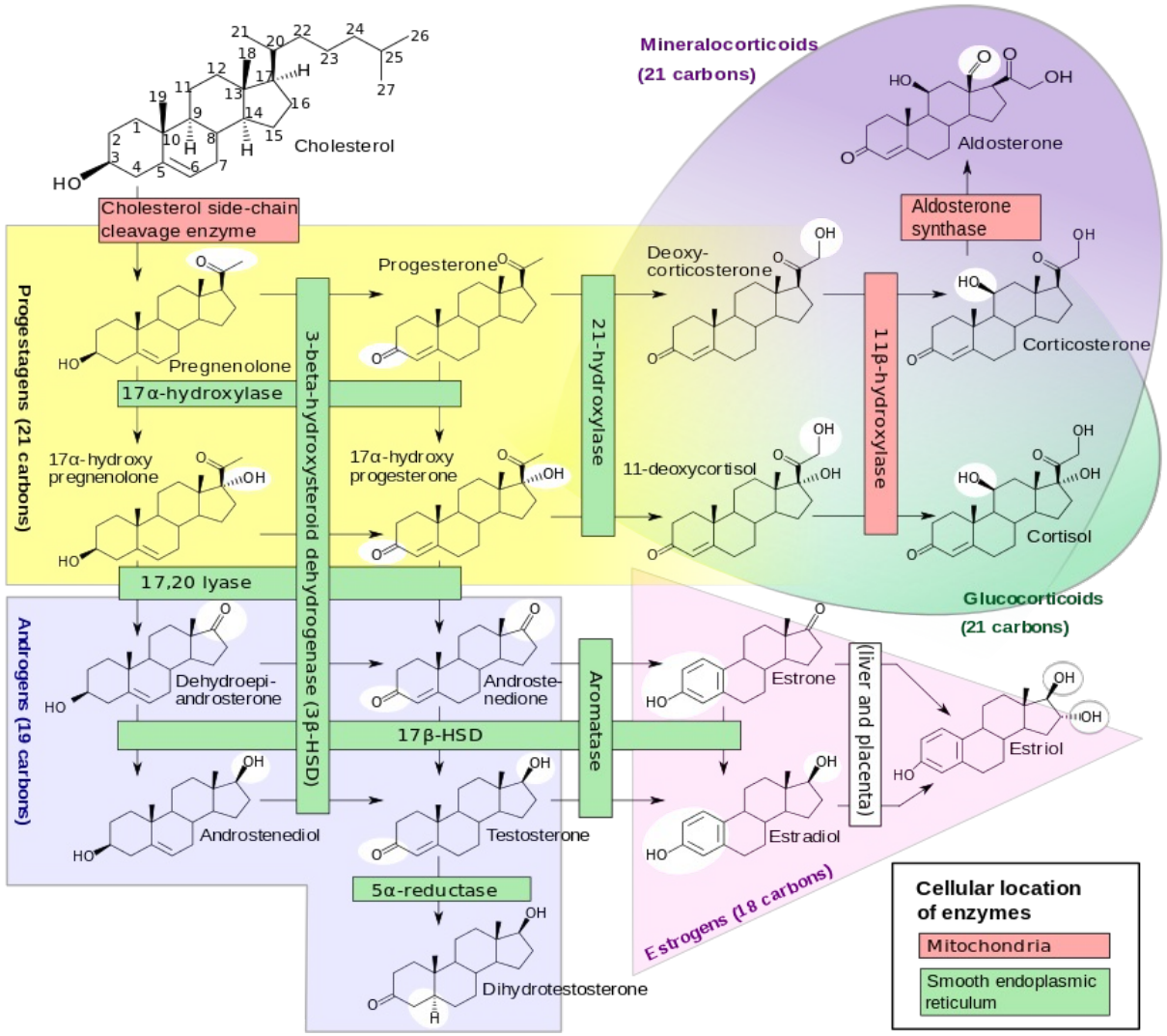
DABCI UNIVERSITY

Steroidogenesis

- A process in which cholesterol is converted to biologically active steroid hormones
  - *Whereas most endocrine texts discuss adrenal, ovarian, testicular, placental, and other steroidogenic processes in a gland-specific fashion, steroidogenesis is better understood as a single process that is repeated in each gland with cell-type-specific variations on a single theme.*

Endocr Rev. 2011 Feb; 32(1): 81–151. Published online 2010 Nov 4.
doi: 10.1210/er.2010-0013

The Name of the Game is Enzymes

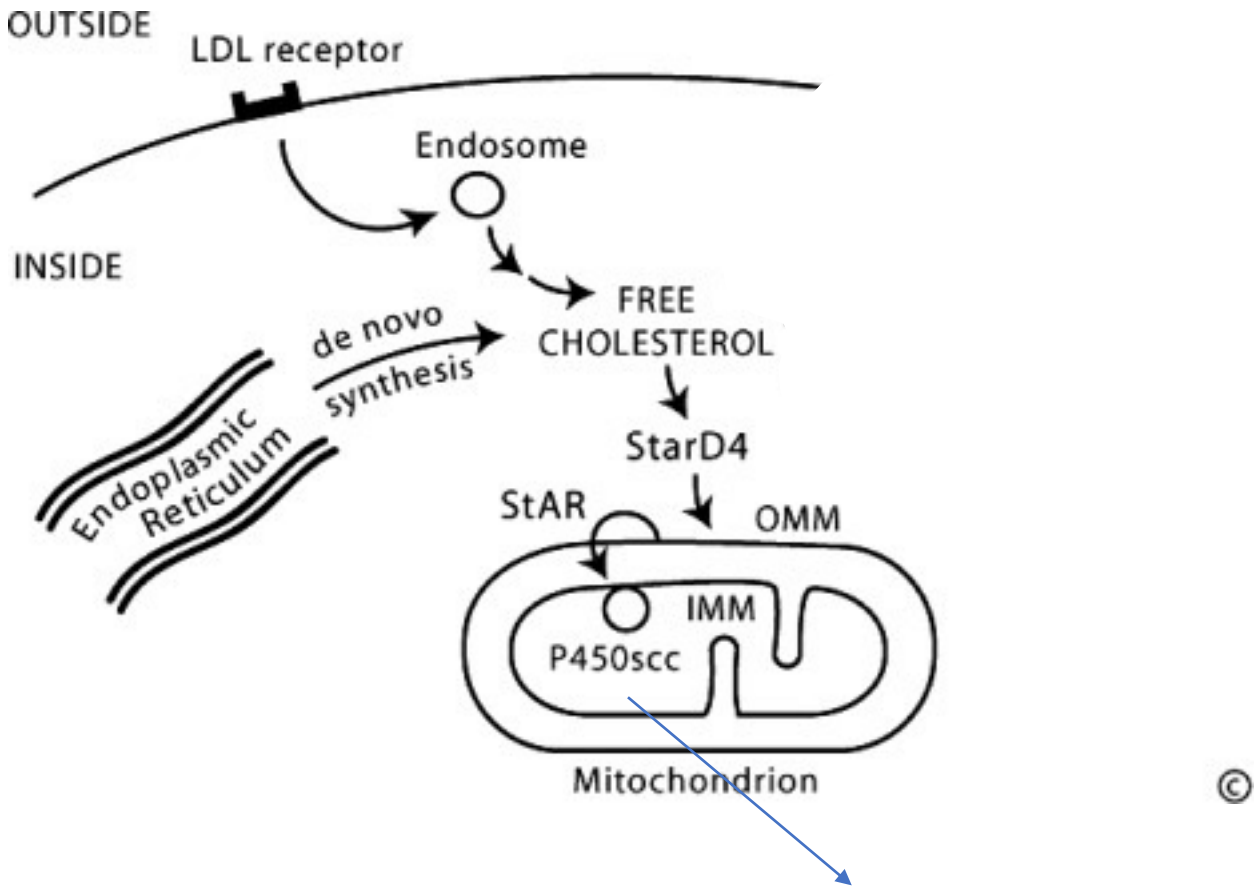


Steroidogenesis

- Rate limiting step is the transport of cholesterol from the cytoplasm to the mitochondria
- Rate limiting enzyme in steroidogenesis
  - CYP450scc(CYP11A1)
- 2 main categories of enzymes involved in the steroid pathways- CYP450 and hydroxy-steroid dehydrogenase (HSD)
- Adrenals can synthesize cholesterol *de novo* from acetate but a majority of cholesterol for steroidogenesis will come from **low-density lipoproteins (LDL)**

Mason JI, Rainey WE. 1987. Steroidogenesis in the human fetal adrenal: a role for cholesterol synthesized de novo. J Clin Endocrinol Metab 64:140–147
Gwynne JT, Strauss JF., 3rd 1982. The role of lipoproteins in steroidogenesis and cholesterol metabolism in steroidogenic glands. Endocr Rev 3:299–329

Steroidogenesis



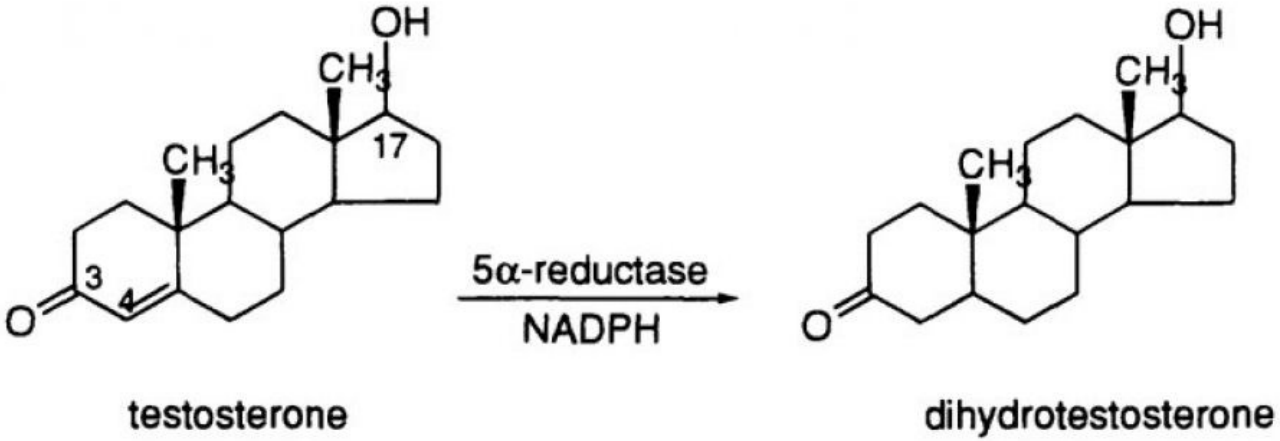
Cholesterol → Pregnenolone

Cholesterol side-chain Cleavage

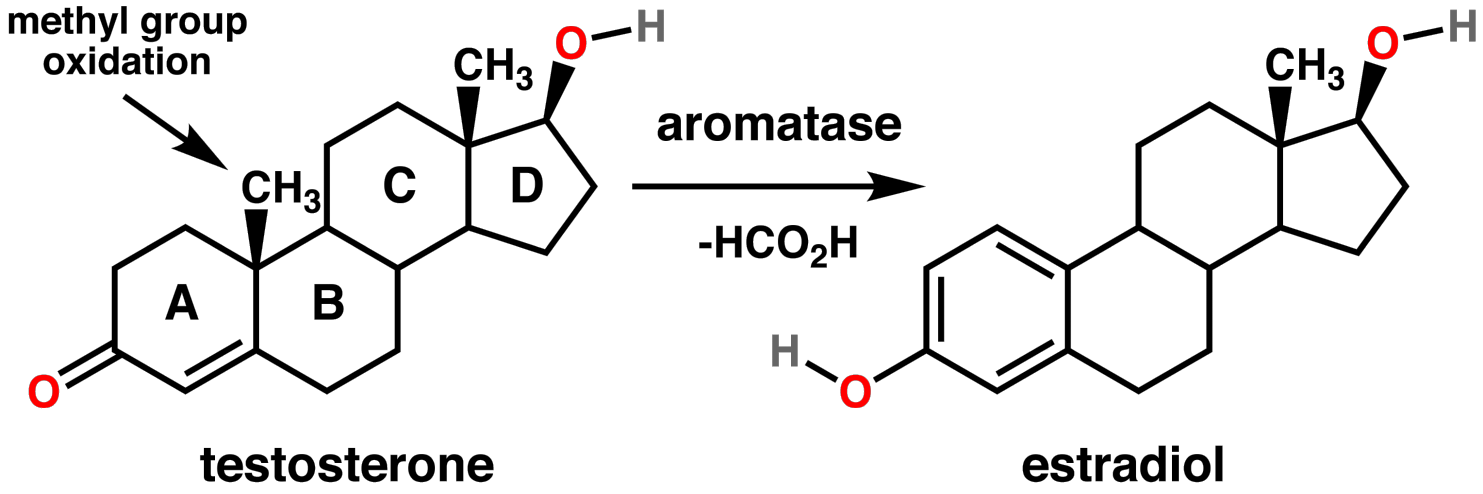
- Highest levels in adrenal, corpus luteum, theca cells and Leydig cells.
- The placenta also expresses high levels of p450scc

Endocr Rev. 2011 Feb; 32(1): 81–151.
Hanukoglu I (December 1992). "Steroidogenic enzymes: structure, function, and role in regulation of steroid hormone biosynthesis". The Journal of Steroid Biochemistry and Molecular Biology. 43 (8): 779–804.
Strauss JF, Martinez F, Kiriakidou M (February 1996). "Placental steroid hormone synthesis: unique features and unanswered questions". Biology of Reproduction. 54 (2): 303–11.

Hormonal Conversions as a Cause of Low Testosterone



testosterone dihydrotestosterone



testosterone estradiol

Natural Aromatase Inhibitors

- Chrysin
- Grape seed extract
- Imbach (white button mushrooms)
- DIM
- Vit D

NATURAL PRODUCTS	COMMONLY FOUND IN	OESTROGEN INHIBITION	TYPE OF ACTION	SOURCES
Grapefruit* juice with majority of effects seen from flavonoids Naringin, Naringenin, & quercetin	Grapefruits	**8.8 to -16.5%** (clinical result)	Inhibitory	27,28
Flaxseed	Flaxseed	**16.15 pmol/L** decrease in E2	Inhibitory	29,30
3,3'-Diindolymethane (**DIM**)	Broccoli and cauliflower	At 300mg/d an increased excretion of **6.98 ng/mg *2-OHE* and 7.47 ng/mg *16-OHE1***	Inhibitory	31**
Calcitriol (**Vitamin D**) (25(OH)D)	Fatty fish, fortified foods (milk, orange juice, cereals), egg yolks, cheese, beef liver	If deficient (<20 ng/ml 25(OH)D) then a difference of **3-8 pmol/L**, if within 20 - < 30 ng/mL 25(OH)D then a difference of **1-6 pmol/L**	Inhibitory (indirectly via SHBG alteration)	32,33
α-Tocopherol **(Vitamin E)**	Vegetable oils, green leafy veg, seeds, nuts	**Significant decrease** in Oestradiol in men	Inhibitory	34
Wheat fibre	Wheat	**Significant reductions** in E1 & E2	Inhibitory	35,36
Coffee and **Caffeine** > 200 mg	Coffee, teas	Not given	Inhibitory	37,38
Indole-3-carbniol (**I3C**)	Broccoli and cauliflower	Not given	Modulatory	26
Chrysin	Honey, propolis, & passion flowers	Mixed results but generally inhibitory	Inhibitory	39

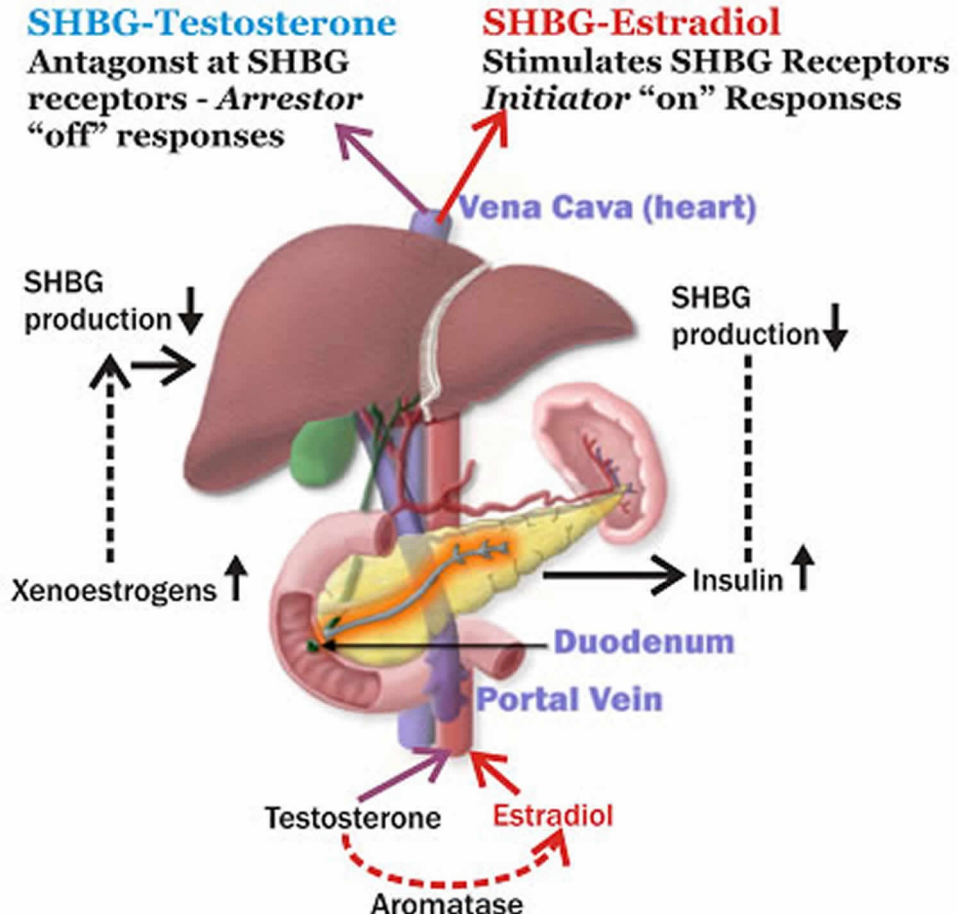
Sex Hormone Binding Globulin (SHBG)

AKA Testosterone-Estradiol Binding Globulin.

- 17-ketosteroids, such as dehydroepiandrosterone (DHEA) and androstenedione, do not bind so easily. SHBG has a high binding affinity to dihydrotestosterone (DHT), medium affinity to testosterone and estradiol, and only a low affinity to estrone, DHEA, androstenedione, and estriol.
- SHBG transports these hormones in the blood as biologically inactive forms. SHBG controls how much of these hormones are delivered to your body's tissues.

Sex Hormone Binding Globulin (SHBG)

- Increased SHBG levels may be associated with symptoms and signs of hypogonadism in men, while decreased levels can result in androgenization in women.
- In men, about 45% to 65% of testosterone in blood is normally bound to SHBG, with the remainder weakly and reversibly bound to albumin

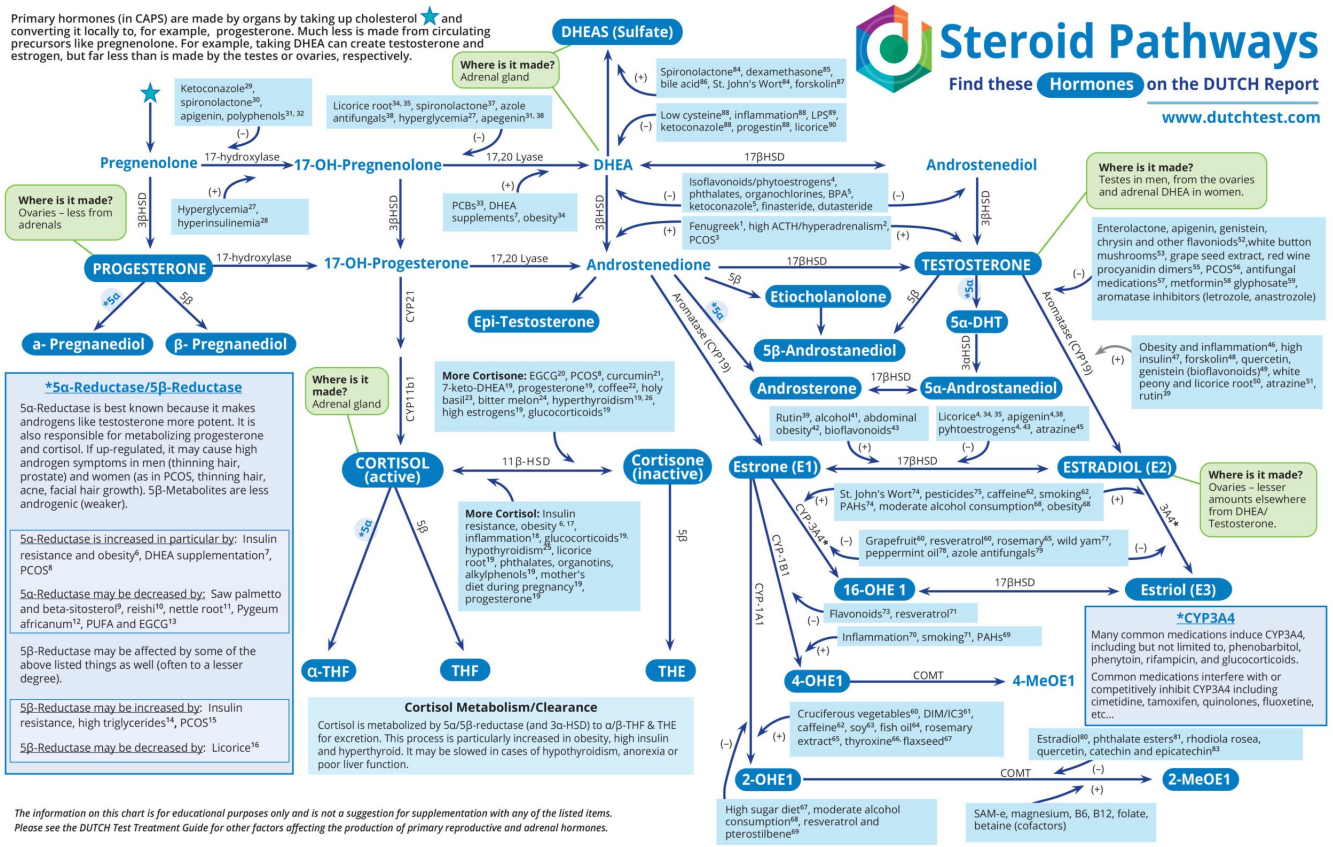


Sex Hormone Binding Globulin (SHBG)

- A slightly increased amount of testosterone (66% to 78%) is bound to SHBG in the blood in women. In the setting of low SHBG, women may have signs and symptoms related to androgen excess.
- If a person's SHBG level is not normal, then the total testosterone may not be an accurate representation of the amount of testosterone that is available to the person's tissues. An SHBG test may be performed when a person's signs and symptoms do not correlate with the results of a total testosterone test.

Sex Hormone Binding Globulin (SHBG)

- Insulin resistance, even without obesity, results in lower SHBG levels. This is associated with increased intra-abdominal fat deposition and an unfavorable cardiovascular risk profile. Insulin resistance and excessive alcohol consumption will accelerate the aromatization of testosterone to E2.



Sex Hormone Binding Globulin (SHBG)

Endogenous or exogenous thyroid hormones or estrogens increase SHBG levels. In men, there is also an age-related gradual rise, possibly secondary to the mild age-related fall in testosterone production.

Decrease SHBG	Increase SHBG
Androgens	Estrogens
Obesity	Pregnancy (Estrogens)
Insulin resistance	Weight loss
Metabolic syndrome	Alcoholic cirrhosis
Type 2 diabetes mellitus	Hepatitis-B and hepatitis-C infection
Gestational diabetes mellitus	Hemochromatosis
Polycystic ovary syndrome	Hyperthyroidism
Non-alcoholic fatty liver disease	Growth hormone deficiency
Acromegaly	Acute intermittent porphyria
Cushing's syndrome	First generation anticonvulsants
Congenital adrenal hyperplasia	
Hyperprolactinemia	
Tumor necrosis factor alpha	
Interleukin-1 beta	

Sex Hormone Binding Globulin (SHBG)

High SHBG symptoms

- Symptoms of low testosterone levels in men include:
- Low sex drive
- Difficulty getting an erection
- Fertility problems

- Treating an elevated SHBG has more to do with finding and treating the underlying cause of the elevation rather than treating the elevated SHBG itself.

Sex Hormone Binding Globulin (SHBG) **Test**

- Free Androgen Index = Total Testosterone / SHBG
- Accurate free testosterone measurement is through equilibrium dialysis-based “true” free testosterone
- SHBG test is used to diagnose and follow-up of women with symptoms or signs of androgen excess (e.g., polycystic ovarian syndrome (PCOS) and idiopathic hirsutism).

- SHBG test is not performed frequently or routinely. In many cases, health practitioners feel that the total testosterone, and perhaps free testosterone (as measured by a method called equilibrium dialysis), provides sufficient information. SHBG is ordered primarily when the total testosterone results do not seem to be consistent with clinical signs and symptoms, such as infertility, decreased sex drive, and erectile dysfunction in men or infertility, irregular menstrual periods, and excess facial and body hair in women.

High SHBG

1. Check your Estrogen and Progesterone Level. If the ratio of estrogen: progesterone is >10:1, you have estrogen dominance that needs to be addressed.

2. Check Your Thyroid Levels. If estrogen levels are normal, then it is highly likely that your thyroid is the culprit of your elevated SHBG. Thyrotoxicosis (hyperthyroidism) increases SHBG levels.

- Check a complete thyroid panel, especially free T3 and free T4.
- Could be an indicator the patient is on too much thyroid hormone.

3. Stop Smoking!

4. If you are on oral birth control pills, consider using another form of birth control –

5. Work on Stress Management

Low SHBG

If SHBG levels are too low, it may mean the sex hormone binding globulin protein is not attaching itself to enough testosterone.

- Symptoms of high testosterone levels in women include:
- Excess body and facial hair growth
- Deepening of voice
- Menstrual irregularities
- Acne
- Weight gain
- Fertility problems

Low SHBG

Many conditions of mild-to-moderate androgen excess in women, particularly polycystic ovarian syndrome (PCOS), are associated with low sex hormone-binding globulin (SHBG) levels. Most of these women are also insulin resistant and many are obese. A defect in SHBG production could lead to bioavailable androgen excess, in turn causing insulin resistance that depresses SHBG levels further.

- Any therapy that either increases SHBG levels (e.g, estrogens or weight loss), reduces bioactivity of androgens (e.g, androgen receptor antagonists, alpha-reductase inhibitors), or reduces insulin resistance (e.g, weight loss, metformin, peroxisome proliferator-activated receptor [PPAR] gamma agonists), can be effective.

Low SHBG

1) Check a complete thyroid panel:

TSH

free T4

free T3

reverse T3

TPO antibodies

thyroglobulin antibodies

- If thyroid function is low, it is probably affecting SHBG level and you will need to consider recommending a thyroid medication and doing other things to help boost your thyroid function.

Low SHBG

- 2. Check estrogen/progesterone ratio if patient is menopausal

After menopause, estrogen levels will drop which can drop SHBG level.

- 3. Check your free testosterone level.

- If SHBG level is low, there will be less of it to bind to testosterone, so it may cause free testosterone level to rise.
- This can usually be alleviated by maximizing thyroid medication which will raise your SHBG level.

Oxytocin

- Produced in then hypothalamus and release by the posterior pituitary.
- It plays a role in social bonding, reproduction, childbirth, and the period after childbirth. Oxytocin is released into the bloodstream as a hormone in response to sexual activity and during labor.

Vasopressin (ADH)

- Produced in then hypothalamus and release by the posterior pituitary.
- ADH has two primary functions. First, it increases the amount of solute-free water reabsorbed back into the circulation from the filtrate in the kidney tubules of the nephrons. Second, ADH constricts arterioles, which increases peripheral vascular resistance and raises arterial blood pressure.
- A third function is possible. Some ADH may be released directly into the brain from the hypothalamus, and may play an important role in social behavior, sexual motivation and pair bonding, and maternal responses to stress.

Oxytocin and Vasopressin (ADH)

- Working together OT and VP, and their receptors, create a biological and genetic pathway that regulates attachment and bonding, which in turn may be protective against threats or other forms of challenge.

- Among the patterns of behavior for which both OT and VP may be necessary are sexual behavior, paternal behavior, and pair bonding

Journal of Autacoids and Hormones

Editorial Open Access

Serotonin and Sexual Dysfunction

GS Shankar

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College of Pharmacy, Western University of Health Sciences, Pomona, CA, 91766-1854

High levels of serotonin tend to indicate a low libido, while low levels of serotonin correspond with a high libido—but that's not the whole story. Technically, whether serotonin inhibits or stimulates your libido depends on which receptors in the brain are activated.

SNRIs target serotonin and norepinephrine to increase the effectiveness of serotonin. This class of serotonin and norepinephrine reuptake inhibitors blocks or delays the reabsorption of both serotonin and norepinephrine. Norepinephrine works along with serotonin and dopamine to regulate emotions and thought processes

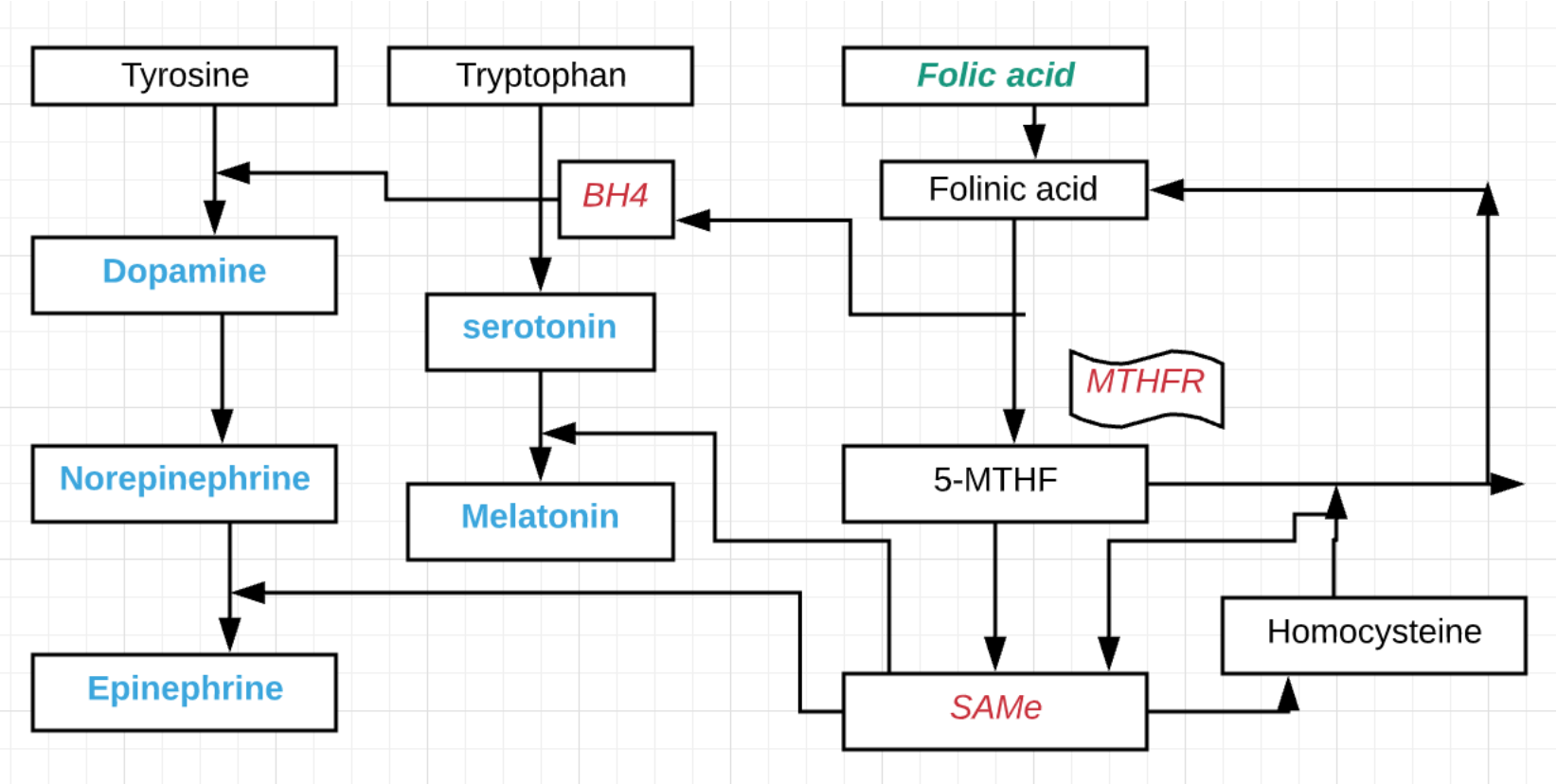
The involvement of dopamine in human sexuality

European Psychiatry
Volume 25, Supplement 1, 2010,
Page 155

Author links open overlay panelZ. Zemishlany [1] [2]

- Studies in humans and animals have suggested that the central dopaminergic system is involved in all components of male and female sexual behavior: desire, erection, orgasm and satisfaction.
- Dopaminergic agonists such as L-dopa, apomorphine, amantadine, bupropion, amphetamines and cocaine have been reported to arouse sexual behavior. Short term use of cocaine and other drugs that increase dopaminergic activity (Marijuana, MDMA) facilitate sexual desire and erection and delay ejaculation.
- Enhancement of dopaminergic activity by the addition of the DA agonists or bupropion, a norepinephrine-dopamine reuptake inhibitor, has been reported as an effective approach in the management of antidepressant-induced sexual dysfunction.

Neurotransmitter Cycle in Methylation Pathway



Interactions between inflammation and female sexual desire and arousal function

Curr Sex Health Rep. Author manuscript; available in PMC 2020 Dec 11.
Published in final edited form as:
Curr Sex Health Rep. 2019 Dec; 11(4): 287–299.
Published online 2019 Oct 28. doi: 10.1007/s11930-019-00218-7
PMCID: PMC7731354NIHMSID: NIHMS1541571 PMID: 33312080

Tierney K. Lorenz

- **Sexual desire** is a motivational state, reflecting the interest in or receptiveness to sexual activity either with or without a partner
- Female **sexual arousal** involves thoughts and emotions as well as physiologic responses including both sympathetic nervous system activation (e.g., increased heart rate, blood pressure, and breathing rate) and arousal of the sex organs (e.g., engorgement of the vulva and vaginal lubrication).
- In healthy females, desire can lead to arousal, and vice versa, in a cyclical feedback loop. Insofar as inflammation influences sexual desire, it will likely also impact arousal.

Heiman JR, Pfaff D. Sexual arousal and related concepts: An introduction. *Horm Behav*. 2011;59(5):613–5. [PubMed]

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Tierney K. Lorenz

Inflammation is a suite of immune processes that respond to pathogens and toxins, identify and clear out damaged cells, and stimulate and direct the adaptive immune system. In the acute phase, stimulated immune cells exert a variety of inflammatory actions: increasing blood flow and permeability of blood vessels to permit diffusion of plasma into the tissues; phagocytosis of pathogens and cellular waste; release of substances such as histamines that damage foreign cells; and generation of acute-phase products such as coagulation factors and complement proteins.

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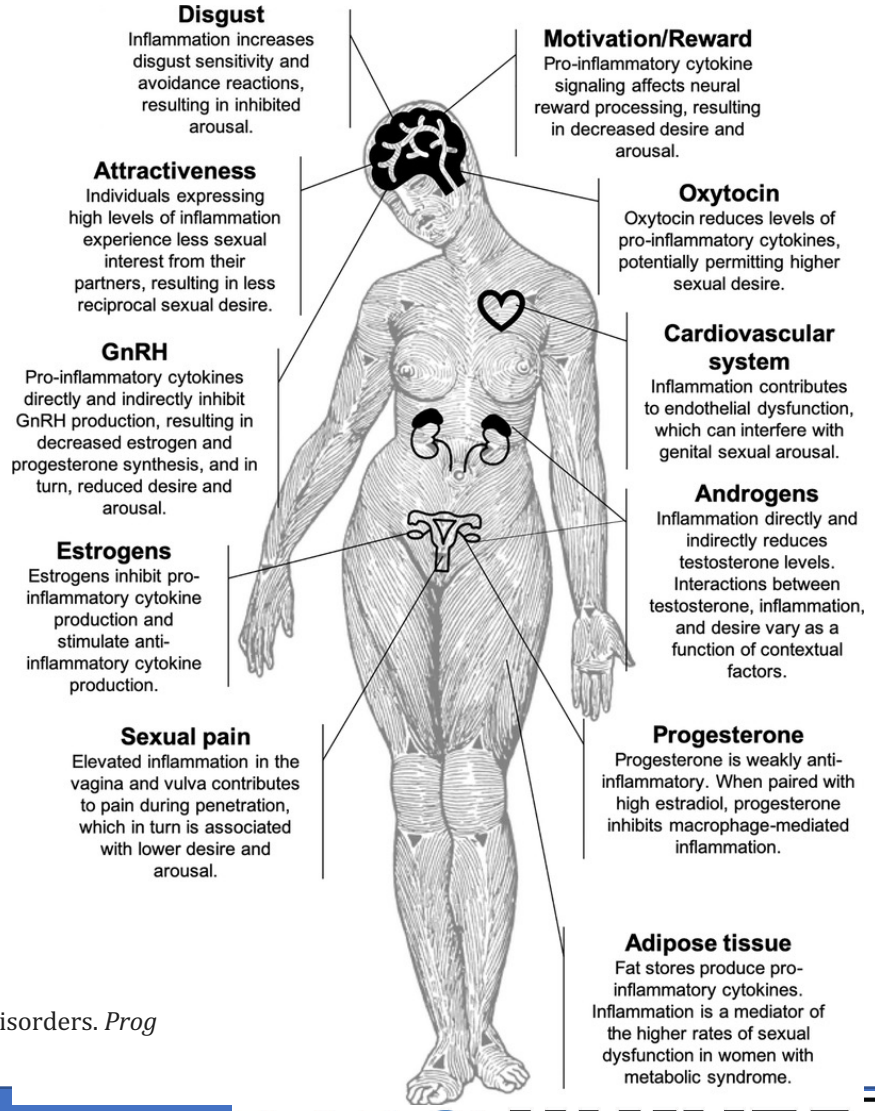
Tierney K. Lorenz

The inflammatory response can evolve to a chronic phase that can result in lasting tissue damage and contributes to future immune hypersensitivity and autoimmunity as well as a number of chronic diseases such as metabolic and mood disorders.



Rosenblat JD, Cha DS, Mansur RB, McIntyre RS. Inflamed moods: a review of the interactions between inflammation and mood disorders. *Prog Neuropsychopharmacol Biol Psychiatry*. 2014;53:23–34.

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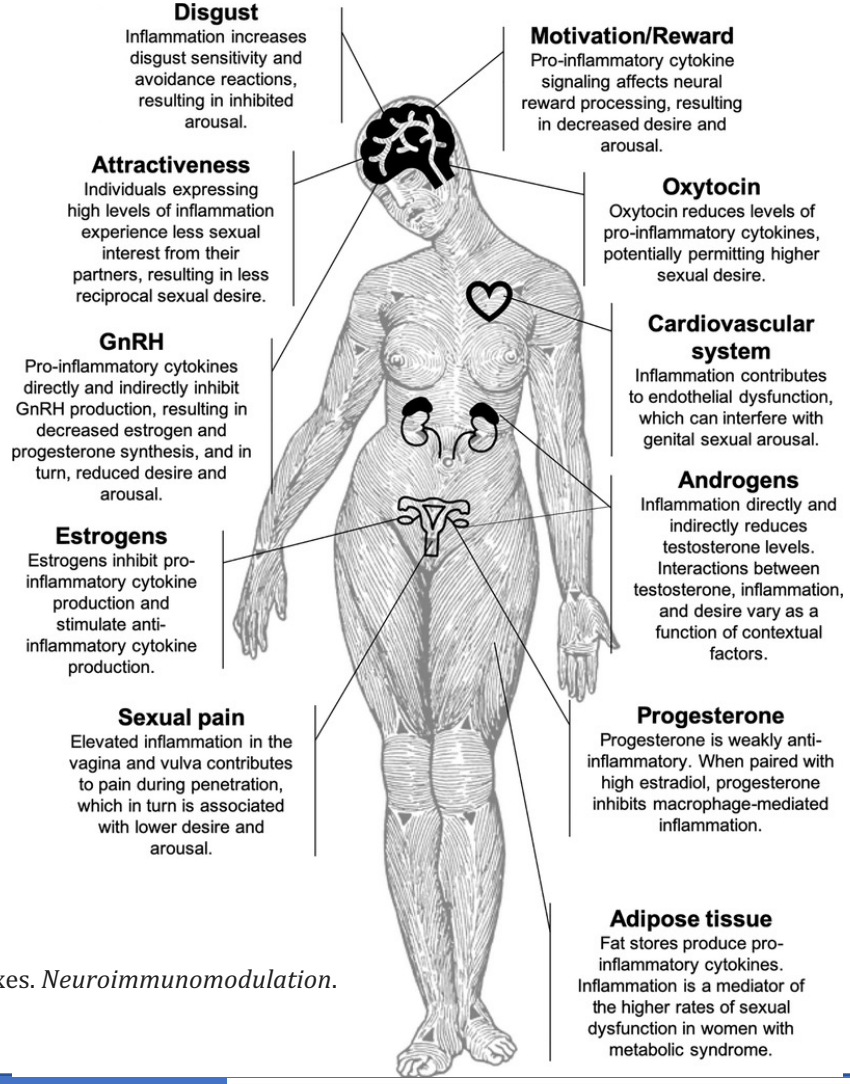
Tierney K. Lorenz

Much research on inflammation indexes the level of cytokines, proteins secreted both by immune cells (e.g., macrophages) and other tissues (e.g., endothelial cells). Like hormones, these proteins act on receptors to produce an effect, including regulating inflammation processes; notably, cytokines can also act on cells outside the immune system such as the nervous system (e.g., neurons and microglia and endocrine system (e.g., gonads)



Spangelo BL, Judd AM, Call GB, Zumwalt J, Gorospe WC. Role of the cytokines in the hypothalamic-pituitary-adrenal and gonadal axes. *Neuroimmunomodulation*. 1995;2(5):299–312.

Interactions between inflammation and female sexual desire and arousal function

Curr Sex Health Rep. Author manuscript; available in PMC 2020 Dec 11.
Published in final edited form as:
Curr Sex Health Rep. 2019 Dec; 11(4): 287–299.
Published online 2019 Oct 28. doi: 10.1007/s11930-019-00218-7
PMCID: PMC7731354NIHMSID: NIHMS1541571 PMID: 33312080

Tierney K. Lorenz

- Another commonly indexed marker of inflammation is C-reactive protein (CRP). Acute-phase proteins like CRP aid in disposal of dead cells and pathogens by binding to their surface and attracting other immune actors to dispose of them.

- Areas of the brain that have been shown to be relevant for coordination of sexual desire and arousal, such as the mesolimbic reward system, cingulate cortex, and thalamus, have been shown to respond to cytokine signaling, both directly on neuronal receptors and indirectly though interactions with dopamine and other neurotransmitters

Felger JC, Miller AH. Cytokine effects on the basal ganglia and dopamine function: The subcortical source of inflammatory malaise. *Front Neuroendocrinol*. 2012;33(3):315–27.

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Tierney K. Lorenz

- At high levels (e.g., during pregnancy) estrogens typically have an anti-inflammatory action, by inhibiting production of pro-inflammatory cytokines and stimulating production of anti-inflammatory cytokines.
- However, at lower levels estrogens can be pro-inflammatory and increase the inflammatory action of neutrophils and monocytes.
- Progesterone is typically weakly anti-inflammatory, but in the presence of high levels of estradiol, can exert powerful inhibitory effects on macrophage-mediated inflammation processes.

Bamberger C, Schulte H. Molecular mechanisms of dissociative glucocorticoid activity. *Eur J Clin Invest.* 2000;30(s3):6–9.

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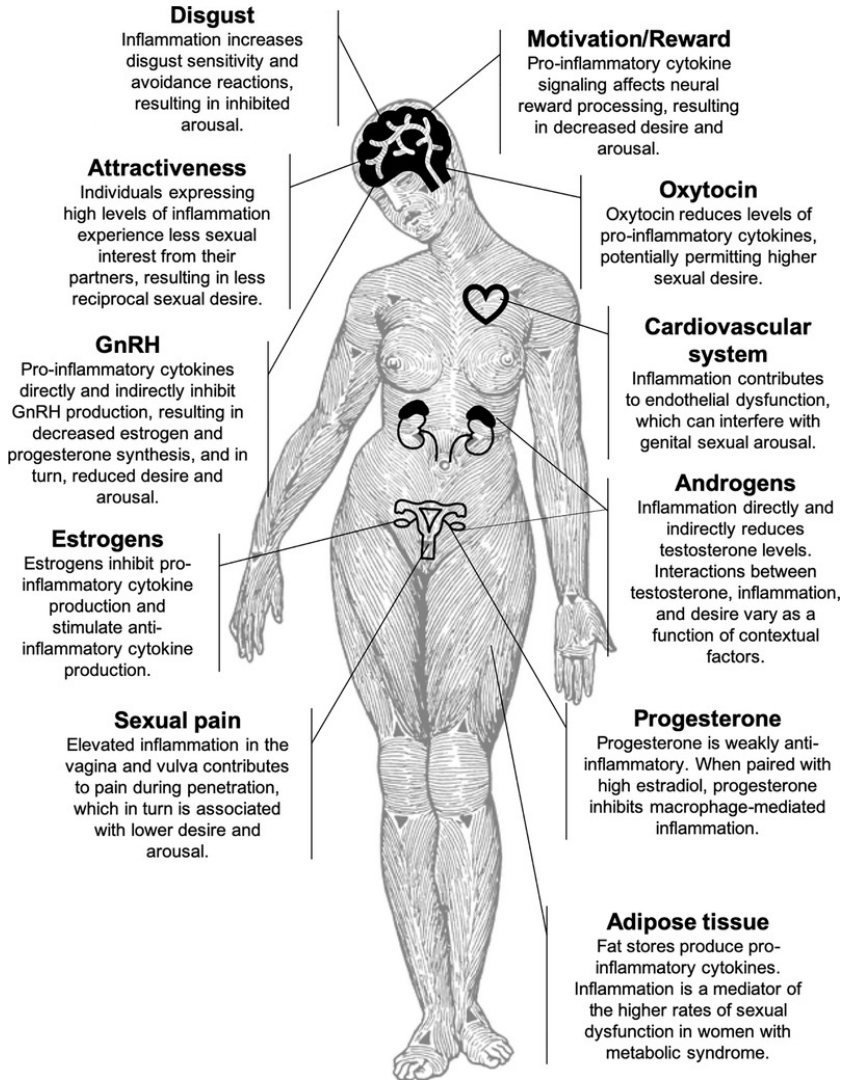
Tierney K. Lorenz

- Chronically high inflammation can interfere with nitric-oxide mediated vasodilation, which is necessary for genital arousal. In males, high levels of TNF-α and IL-6 are associated with erectile dysfunction.
- Specifically, TNF-α has been demonstrated to reduce synthesis of nitric oxide in erectile tissue.



Carneiro FS, Sturgis LC, Giachini FRC, Carneiro ZN, Lima VV, Wynne BM, et al. TNF-α Knockout Mice Have Increased Corpora Cavernosa Relaxation. *The Journal of Sexual Medicine*. 2009;6(1):115–25.

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Tierney K. Lorenz

In Conclusion:

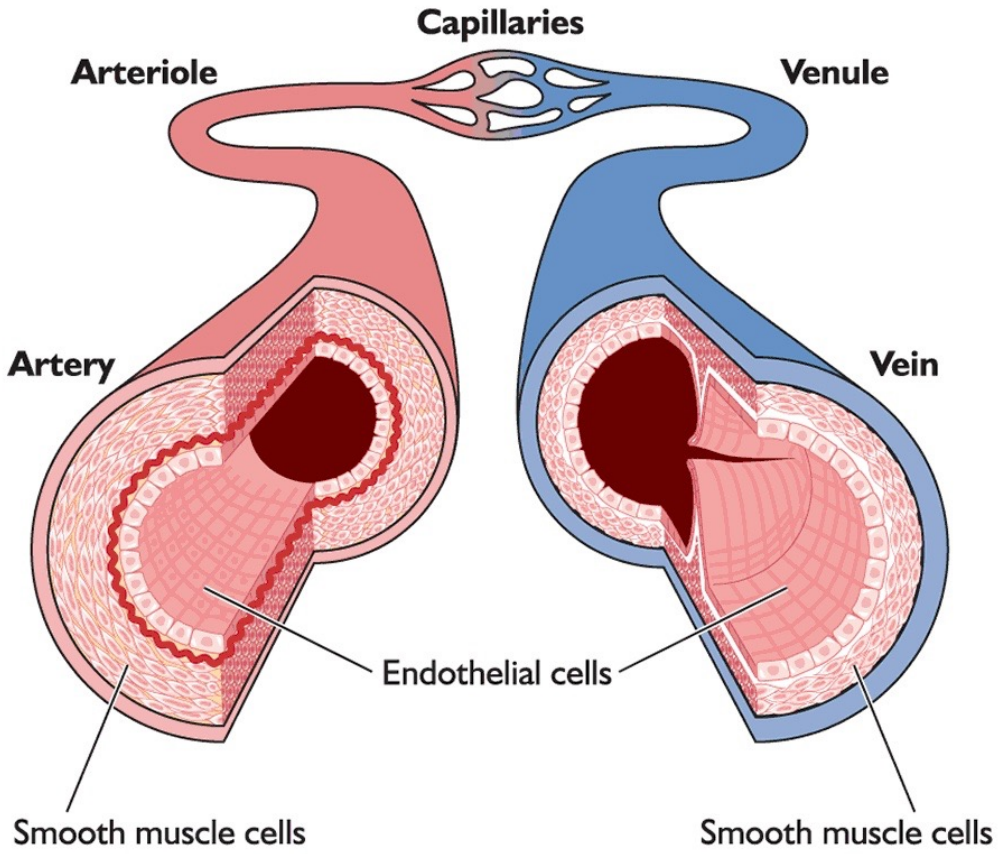
Preliminary data strongly suggest that anti-inflammatory diets improve sexual desire and arousal, particularly among overweight women; given their high potential benefit and low risk of harm, these diets may be recommended as a preventive first-line treatment or adjunctive to treatments for sexual desire or arousal concerns.

The aggregate evidence suggests that inflammation may interfere with female sexual desire and arousal by both direct (neural) and indirect (endocrine, endothelial, social/behavioral) mechanisms.

Erectile Dysfunction (ED) as a Result of Endothelial Dysfunction

The Endothelium

Thin layer of cells that lines the interior surface of blood vessels and lymphatic vessels forming an interface between circulating blood or lymph in the lumen and the rest of the vessel wall.



The Endothelium

- Vascular endothelial cells line the entire circulatory system, from the heart to the smallest capillaries. Endothelial cell functions include fluid filtration, such as in the glomeruli of the kidney, blood vessel tone, hemostasis, neutrophil recruitment, and hormone trafficking.
- Endothelium of the interior surfaces of the heart chambers are called endocardium.

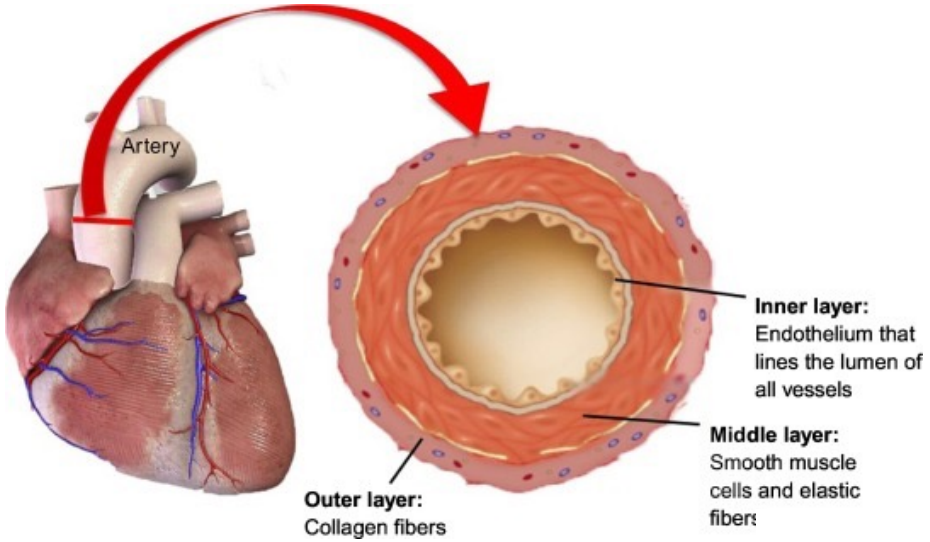
Endothelial Functions

- 1) Barrier Function: the endothelium acts as a semi-selective barrier between the vessel lumen and surrounding tissue, controlling the passage of materials and the transit of white blood cells into and out of the bloodstream.
- 2) Blood clotting: The endothelium normally provides a non-thrombogenic surface because it contains, for example, heparan sulfate which acts as a cofactor for activating antithrombin, a protease that inactivates several factors in the coagulation cascade.

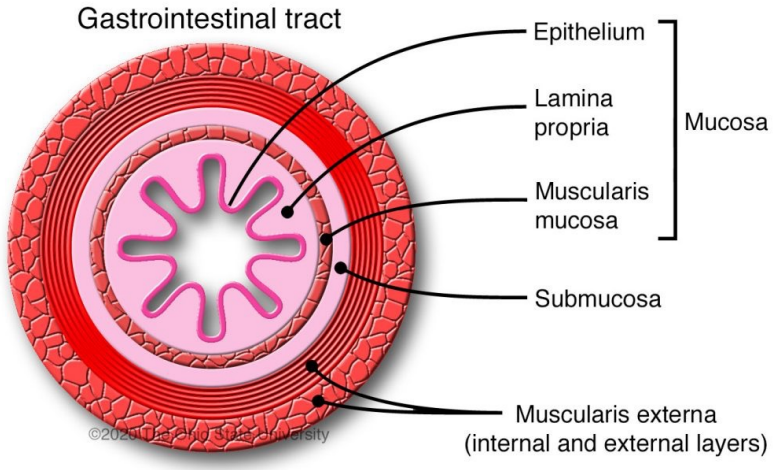
Endothelial Functions

- 3) Angiogenesis: the formation of new blood vessels.
- 4) Vasoconstriction and vasodilation and therefore the control of blood pressure.
- Endothelial dysfunction is a hallmark for vascular diseases and is often regarded as a key early event in the development of atherosclerosis. Endothelial dysfunction has also been shown to be predictive of future adverse cardiovascular events and is also present in inflammatory disease such as rheumatoid arthritis and systemic lupus erythematosus.

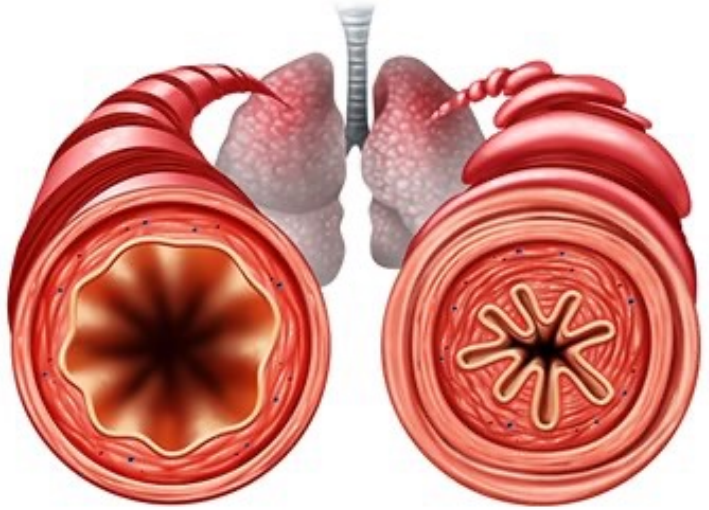
Tubular Organ Systems



Artery



Intestine



Bronchi

The Endothelium

The development of atherosclerosis is a complex interaction between genetic predisposition, CAD risk factors, endothelial dysfunction, lipid accumulation of oxidized LDL, vascular inflammation and arterial thrombosis.

Helps regulate

1)permeability of the vessel

2) stickiness

3) BP

Nitric Oxide

- Formerly called endothelial derived relaxing factor
- Has a half life of only a few seconds
- Has only a local effect
- Produces by Nitric Oxide Synthase

- Cytokines, acetylcholine and various other signaling molecules can trigger the production of NO.
- Nitric oxide is a signaling molecule that ultimately dilates blood vessels
- Endothelial cells pick up on sheer stress and pressure
- Nitric oxide will diffuse into the smooth muscle layer and cause it to relax

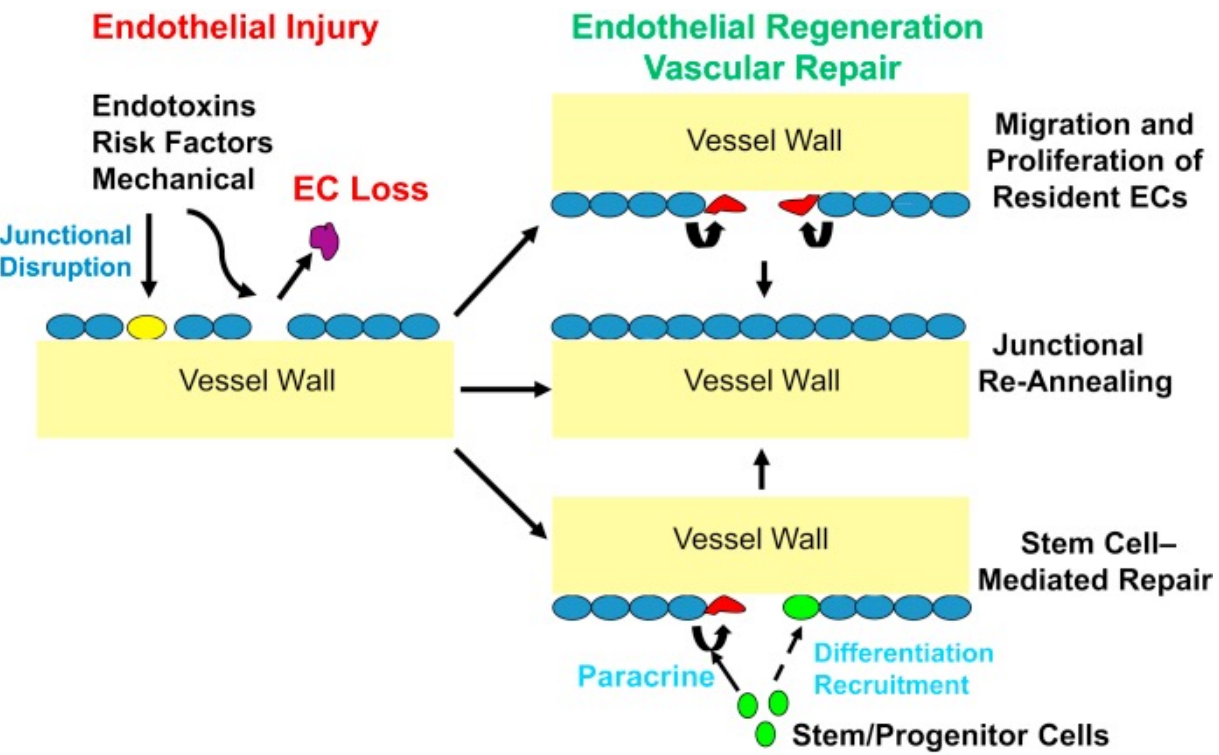
Endothelial Dysfunction: Cardiovascular Risk Factors, Therapy, and Outcome

Hadi AR Hadi, Cornelia S Carr, and Jassim Al Suwaidi

Vasc Health Risk Manag. 2005
Sep; 1(3): 183–198.
Published online 2005 Sep.

Endothelial dysfunction is a well-established response to cardiovascular risk factors and precedes the development of atherosclerosis. Endothelial dysfunction is involved in lesion formation by the promotion of both the early and late mechanisms of atherosclerosis including up-regulation of adhesion molecules, increased chemokine secretion and leukocyte adherence, increased cell permeability, enhanced low-density lipoprotein oxidation, platelet activation, cytokine elaboration, and vascular smooth muscle cell proliferation and migration. Endothelial dysfunction is a term that covers diminished production/availability of nitric oxide and/or an imbalance in the relative contribution of endothelium-derived relaxing and contracting factors. Also, when cardiovascular risk factors are treated the endothelial dysfunction is reversed and it is an independent predictor of cardiac events.

Endothelial Regeneration



Processes of endothelial regeneration and vascular repair. Endothelial injury induced by inflammatory or mechanical stimuli as well as risk factors are characterized by endothelial cell (EC) death and/or disruption of endothelial cell-cell junctions, leading to increases in vascular permeability. The vascular repair process involves restoration of a functional endothelial monolayer (ie, endothelial regeneration) and reannealing of the endothelial junctions to restore a semipermeable barrier. Endothelial regeneration is primarily attributable to migration and proliferation of resident ECs. Evidence of bone marrow–derived stem/progenitor cell engraftment is limited (**dashed line**), but these cells can contribute to endothelial regeneration in a paracrine manner through the release of regenerative/reparative factors.

Journal of Nutritional Science and Vitaminology

Inhibitory Effect of δ-Tocotrienol, a HMG CoA Reductase Inhibitor. on Monocyte-Endothelial Ce Adhesion

Jun-Tzu CHAO, Abdul GAPOR, Andre THERIAULT

- One of the first steps in atherogenesis is fatty streak formation in arteries, which begins with the adherence of circulating monocytes to the endothelium. Tocotrienols have been shown to reduce cellular adhesion molecule expression and monocyte adherence.
- In particular , delta-tocotrienol showed the most profound effect on monocyte adherence compared to tocopherols and other tocotrienol isomers.
- Delta and gamma tocotrienols were 60x and 30x more potent than alpha tocopherol, respectively.

DABCI UNIVERSITY

Supplementation for Endothelial Dysfunction

- L Arginine
- Magnesium
- Vit C
- CO Q 10
- Lipoic Acid
- Resveratrol
- Vit E
- Omega 3 fatty acids
- Flavonoids
- Lipoic acid
- SOD and Catalase

Sexual dysfunction in selective serotonin reuptake inhibitors (SSRIs) and potential solutions: A narrative literature review

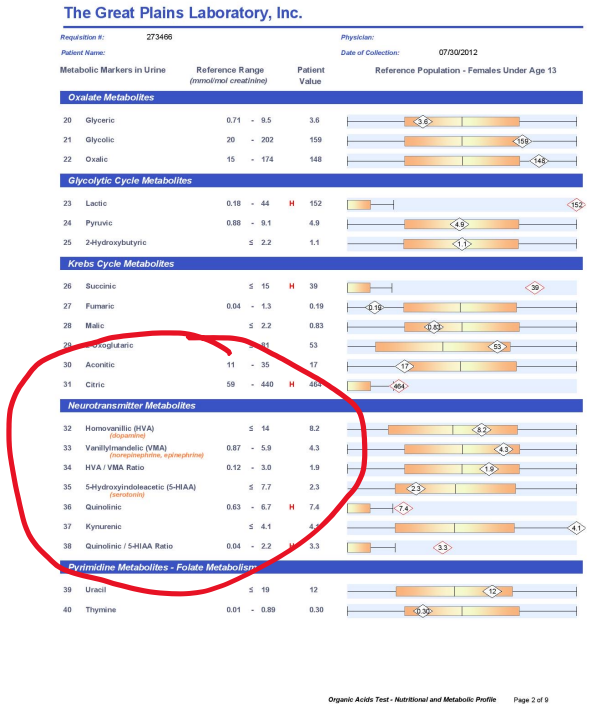
Ment Health Clin. 2016 Jul; 6(4): 191–196
Elizabeth Jing, BS [1] and Kristyn Straw-Wilson, PharmD, BCPP[2]

Published online 2016 Jun 29. doi: 10.9740/mhc.2016.07.191

- This study evaluated primary literature from 1997 to 2015 to identify SSRI-related sexual side effects, therapeutic alternatives, and treatment strategies.
- Given the prevalence of sexual dysfunction in subjects with depression, it is necessary for health care providers to give a full assessment and explanation of potential side effects of antidepressant pharmacotherapy. For sexually active subjects requiring an SSRI, it is recommended to first try fluoxetine or sertraline, as they have less incidence of causing sexual dysfunction.
- Paroxetine should be the last SSRI of choice as it has the greatest incidence of causing sexual dysfunction.
- Other nontraditional methods for alleviating sexual side effects, such as the supplementation of saffron 15 mg twice a day, may improve arousal and erectile function in subjects experiencing SSRI-related sexual dysfunction. However, given the limited research on saffron, other therapies should be tried first.

Suggested Lab testing for Low Libido

- Prolactin
- CBC ferritin/Iron panel
- EBV panel, Mycoplasma IgM and IgG
- Thyroid panel with autoantibodies
- Dutch complete
- Organic acid test (OATS)
- Sex Hormone Binding Globulin (SHBG)
- FSH/LH
- ANA Lupus , Sjogrens etc



The Great Plains Laboratory, Inc.

Requisition #: 273466 Physician:

Patient Name: Date of Collection: 07/30/2012

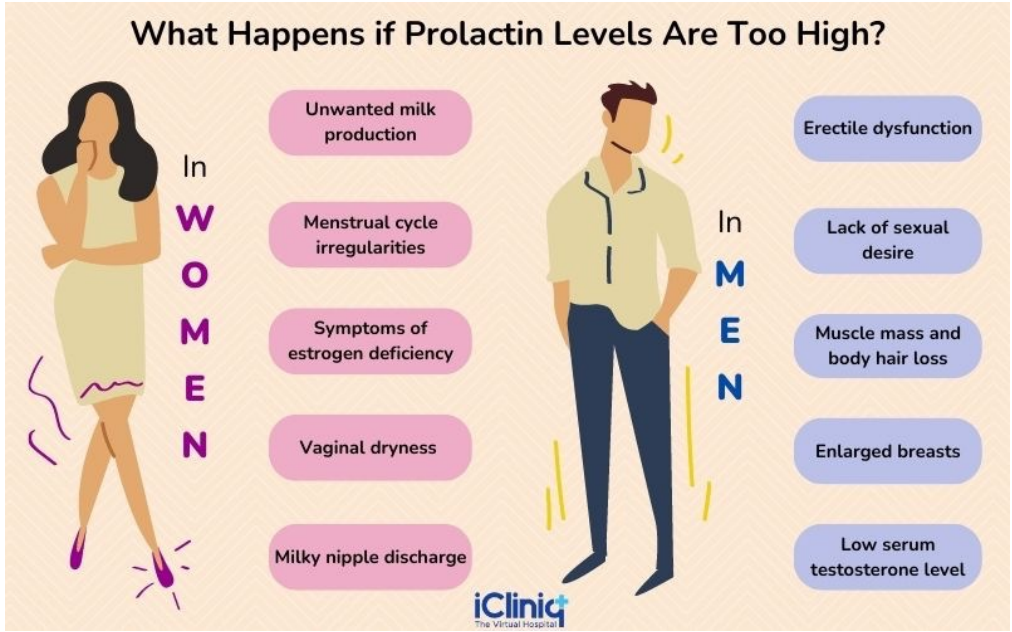
	Metabolic Markers in Urine	Reference Range (mmol/mol creatinine)			Patient Value	Reference Population - Females Under Age 13
Oxalate Metabolites						
20	Glyceric	0.71	-	9.5	3.6	3.6
21	Glycolic	20	-	202	159	159
22	Oxalic	15	-	174	148	148
Glycolytic Cycle Metabolites						
23	Lactic	0.18	-	44	H 152	152
24	Pyruvic	0.88	-	9.1	4.9	4.9
25	2-Hydroxybutyric		≤	2.2	1.1	1.1
Krebs Cycle Metabolites						
26	Succinic		≤	15	H 39	39
27	Fumaric	0.04	-	1.3	0.19	0.19
28	Malic		≤	2.2	0.83	0.83
29	2-Oxoglutaric		≤	94	53	53
30	Aconitic	11	-	35	17	17
31	Citric	59	-	440	H 464	464
Neurotransmitter Metabolites						
32	Homovanillic (HVA) (dopamine)		≤	14	8.2	8.2
33	Vanillylmandelic (VMA) (norepinephrine, epinephrine)	0.87	-	5.9	4.3	4.3
34	HVA / VMA Ratio	0.12	-	3.0	1.9	1.9
35	5-Hydroxyindoleacetic (5-HIAA) (serotonin)		≤	7.7	2.3	2.3
36	Quinolinic	0.63	-	6.7	H 7.4	7.4
37	Kynurenic		≤	4.1	4.1	4.1
38	Quinolinic / 5-HIAA Ratio	0.04	-	2.2	H 3.3	3.3
Pyrimidine Metabolites - Folate Metabolism						
39	Uracil		≤	19	12	12
40	Thymine	0.01	-	0.89	0.30	0.30

Organic Acids Test - Nutritional and Metabolic Profile Page 2 of 9

Prolactin

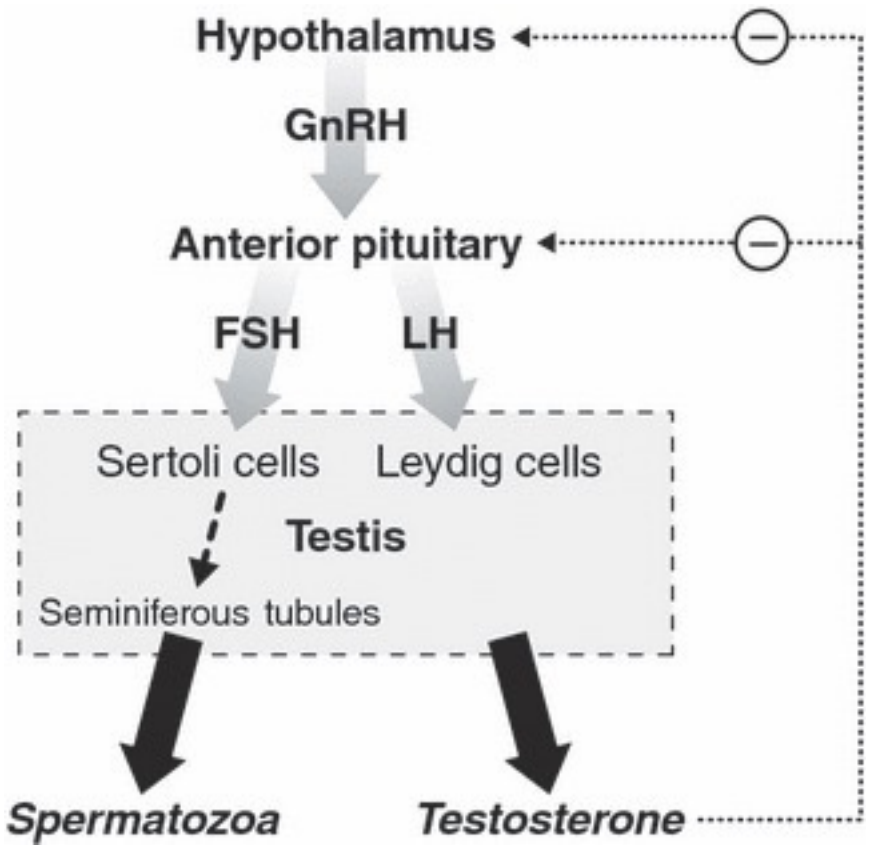
When prolactin levels rise substantially in men, they can significantly affect sexual function. Research has shown that **severe hyperprolactinemia (usually greater than 35 ng/mL) has been linked to low libido and delayed ejaculation in men**. High prolactin might also interfere with testosterone production and erections.

- Dopamine helps suppress the production of prolactin.



FSH and LH in Men

In men, LH stimulates testosterone production from the interstitial cells of the testes (Leydig cells). FSH stimulates testicular growth and enhances the production of an androgen-binding protein by the Sertoli cells, which are a component of the testicular tubule necessary for sustaining the maturing sperm cell.



Medications that Inhibit Sexual Desire/Function

1) **Antidepressants**: Of the SSRIs, paroxetine (Paxil) is most likely to cause sexual problems. Other SSRIs, such as fluvoxamine (Luvox), sertraline (Zoloft), and fluoxetine (Prozac), may also be more likely to cause sexual problems.

Sexual dysfunction is less likely with some other antidepressants. These include mirtazapine (Remeron) and bupropion (Wellbutrin).

2) **Heart failure medications**: Digoxin, Spironolactone, Beta blockers

3) **Blood Pressure medications**: clonidine, Beta blockers, Spironolactone

Medications that Inhibit Sexual Desire/Function

4) **H2 Blockers**: cimetidine (Tagamet), Famotidine (Pepcid AC, Zantac 360)

5) **Cancer treatments/ radiation treatments**

6) **Medications that affect sex hormones** such as estrogen, testosterone, and progesterone. Birth control pills.

7) **Antipsychotics**: Antipsychotic medications treat various mental health conditions like schizophrenia and bipolar disorder. Risperdal, Haldol

Medications that Inhibit Sexual Desire/Function

8) **Opioids**: include tramadol (Ultram) and Norco (hydrocodone/acetaminophen).

9) **Benzodiazepines**: include alprazolam (Xanax), lorazepam (Ativan), and diazepam (Valium).

10) **Statins**

11) **Antiepileptics**: They include carbamazepine (Tegretol), valproic acid, and phenytoin (Dilantin). Levetiracetam (Keppra) may cause less sexual side effects than other antiepileptics.

Table 1 **Drugs associated with sexual dysfunction** [1-3]

Drug class	Decreased desire	Decreased arousal	Orgasm or ejaculatory difficulties
Antidepressants	amitriptyline clomipramine fluoxetine imipramine paroxetine phenelzine sertraline	amitriptyline citalopram clomipramine doxepin fluoxetine imipramine nortriptyline paroxetine phenelzine sertraline tranylcypromine	citalopram clomipramine doxepin escitalopram fluoxetine* fluvoxamine imipramine nortriptyline paroxetine* sertraline* tranylcypromine venlafaxine
Other psychotropic drugs	alprazolam chlorpromazine fluphenazine haloperidol lithium risperidone	chlorpromazine fluphenazine lithium risperidone	alprazolam fluphenazine haloperidol risperidone
Cardiovascular drugs	clonidine digoxin hydrochlorothiazide methyldopa spironolactone	beta blockers clonidine digoxin hydrochlorothiazide methyldopa perhexilene spironolactone	
Other drugs	cimetidine	antihistamines cimetidine cyproterone disulfiram gonadotrophin-releasing hormone agonists propantheline pseudoephedrine	naproxen

* common cause of orgasmic difficulty

Summary of medications that inhibit libido

Physical Barriers to Normal Libido

- Dyspareunia: pain before ,during or after intercourse.
- Vaginal dryness Wise Woman Vaginal suppositories
- Pyronines
- **Sexual anhedonia, also known as pleasure dissociative orgasmic disorder**, is a condition in which an individual cannot feel pleasure (see anhedonia) from an orgasm. It is thought to be a variant of hypoactive sexual desire disorder.

CNS Neuroscience & Therapeutics

A double-blind, randomized, pilot dose-finding study of maca root (L. meyenii) for the management of SSRI-induced sexual dysfunction

Christina M Dording[1], Lauren Fisher, George Papakostas, Amy Farabaugh, Shamsah Sonawalla, Maurizio Fava, David Mischoulon

We sought to determine whether maca, a Peruvian plant, is effective for selective-serotonin reuptake inhibitor (SSRI)-induced sexual dysfunction. We conducted a double-blind, randomized, parallel group dose-finding pilot study comparing a low-dose (1.5 g/day) to a high-dose (3.0 g/day) maca regimen in 20 remitted depressed outpatients.

- Maca was well tolerated. Maca root may alleviate SSRI-induced sexual dysfunction, and there may be a dose-related effect. Maca may also have a beneficial effect on libido.

Testosterone Treatment

- Peruvian MACA
- Velvet deer antler
- Rhodiola
- Damiana
- Ginkgo
- American Panax Ginseng
- Stinging Nettle

Aterioscler Thromb Vac Biol 1996; 16:749-54.
Am J Ther 1999; 6:167-74. 3.
J Clin Endocrinol Metab 1997; 82:682-5.
Diabetes 1996;45:1605-9.
Int J Cariol 1998;63:161-4.
Am J Epidemiol 1997;146:609-17.

In Summary

- Normal Libido is impossible to define. Multifactorial.
- Do your DABCI work: look at the big picture with a through consultation/case history. Libido problems have many causes.
- In general, healthy people have healthy libidos.

Rule out serious pathology. “Never go with a lesser diagnosis till the more serious diagnosis has been ruled out” Dr. Jack