Scientific Research Publishing

Open Journal of Endocrine and Metabolic Diseases, 2019, 9, 35-48
http://www.scirp.org/journal/ojemd
ISSN Online: 2165-7432
ISSN Print: 2165-7424

The Regulatory Effect of Biogenic Polyamines Spermine and Spermidine in Men and Women

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How to cite this paper: Bendera, R. and Wilson, L.S. (2019) The Regulatory Effect of Biogenic Polyamines Spermine and Spermidine in Men and Women. *Open Journal of Endocrine and Metabolic Diseases*, **9**, 35-48.
https://doi.org/10.4236/ojemd.2019.93004

Received: January 6, 2019
Accepted: March 2, 2019
Published: March 5, 2019

Abstract

Background—The incidence and prevalence of infertility and sexual dysfunction in men and women is increasing. The biogenic polyamines spermine and spermidine are important for sexual function as well as fertility. Spermine and spermidine are present in plant foods and synthesized from ornithine and methionine in mammals. Stress and stress-associated hormone disruption are contributors to both poor sexual function and infertility. Spermine and spermidine are important in reducing the impact of stress on living organisms. ***Objective***—This open-label pilot trial was designed to determine the impact of spermine and spermidine supplementation on hormone levels of otherwise healthy human subjects with no history of infertility or sexual dysfunction over a 30-day period. Pre and post supplement levels of cortisol, DHEAS, testosterone, progesterone and estradiol as well as 30-day post supplement levels of these hormones were performed on age/gender equivalent subjects. A total of 15 individuals participated in the study. Informed consent forms were executed along, with adverse events reporting information. ***Results***—Clinically significant reductions (p-value less than 0.05) in cortisol were seen in 30 days among 83% of male participants and 37% of female participants. Sixty-six percent of male participants maintained lower cortisol levels 30 days after withdrawal of the study supplement. In women, the cumulative effect of the spermine and spermidine supplementation continued with 50% reporting a significant reduction in cortisol levels 30 days after withdrawal of the study supplement. There was an average of 3.3 pounds of weight loss during the first 30 days of supplementation without any dietary or metabolic intervention. Further, 7 out of 8 female participants demonstrated a moderate increase in DHEAS at 30 days, while 5 out of 7 male participants demonstrated a significant Dehydroepiandrosterone (DHEAS) increase in 60 days. Eighty-three percent of men had a decrease in estradiol and 100% of men had a decrease of progesterone at 30 days while 75% of women in follicular phase experienced both an increase in estradiol and a significant increase in progesterone. In the men under 50 years age group, testosterone

levels increased by an average of 48.9% (28.3 pg/mL), while in the over 50 age group, testosterone levels decreased by a mean average of 36.7% (33 pg/mL). In women, 75% had an average increase of 48.8% (10.6 pg/mL) in testosterone levels at 30 days while the same number (75%) had an average decrease of 32.7% (10.5 pg/mL) in testosterone levels at 60 days. ***Conclusion***—For both fertility and sexual performance, it is important to reduce cortisol levels. Also important to fertility is the balancing of various hormone ratios during reproductive years. Likewise, it is important for sexual performance of women post-menopause and men post-andropause to achieve cortisol reduction and hormone balance. The biogenic polyamines spermine and spermidine appear to support a trend toward hormone balance, though a larger trial is needed to confirm this conclusion.

Keywords

Hormones, Hormonal Balancing

1. Background

The biogenic polyamines spermine and spermidine are ubiquitous in plants since they are part of prokaryotic and eukaryotic stress response. They are present in mammalian tissues as well. In humans and other mammals, spermine and spermidine are synthesized from the amino acids ornithine and methionine [1] [2] [3] [4] [5]. In 2006, Jakszyn and Gonzalez reported that spermine and spermidine participate with nitric oxide synthesis, making spermine and spermidine critical to reproduction. Salts of spermine were first isolated in seminal fluid by Leeuwenhoek in 1677 [6].

Polyamines provided by food seem to be essential for the maintenance of normal growth and maturation [7] [8]. Dietary polyamines are associated with cellular growth and differentiation. This association was reported to be due to polyamine interaction with DNA, RNA, and proteins [2] [8]. Furthermore, exogenous polyamines modulate mucosal proliferation and absorption from diet [9]. Hence, insufficient polyamine intake could hinder important health enhancing effects of polyamines such as induction of tolerance to dietary allergens [10]. A high intake of spermine is associated with a decreased risk of food allergy among suckling rats as well as in children, due to the contribution of spermine to maturation of both the immune system [3] [11] and the small intestinal mucosa [12].

Dietary polyamines provide both antioxidant and anti-inflammatory properties [13] [14]. The antioxidant activity of polyamines has been shown to be even stronger than that of some antioxidant vitamins [14].

2. Methods

Saliva samples were collected from each participant at baseline, following 30 days of supplementation (tablet) with spermine and spermidine and 30 days fol-

lowing the withdrawal of the study supplement.

Saliva samples were stored at −70˚C prior to analysis. Samples were thawed and particulate matter removed by centrifugation. 500 ul of each sample was transferred to a 96-well polypropylene block along with 50 ul of PBS buffer. Saliva was then transferred from the blocks onto assay plates for progesterone, testosterone, DHEA-S, and cortisol. The extraction process concentrates the samples and removes potential interference for increased accuracy and precision, which is needed only for estradiol. Cortisol and testosterone are tested by luminescence immunoassays and progesterone, DHEA-S, and estradiol are tested by enzyme immunoassay. Each 96-well block of samples included two blanks and 11 other control samples.

For estradiol analysis, 1.4mL of sample was applied to C18 solid phase extraction columns and eluted with ethanol (500 uL). The estradiol-containing elution was dried under nitrogen (Turbovap-96) and reconstituted with 481 uL of buffer. Estradiol was assayed as for progesterone with slight alterations. Conjugate was added after a 15-minute incubation with only samples, calibrators, and controls at room temperature. The incubation with conjugate was 2 hours, and only 100 ul of substrate was used. For progesterone, 100 ul of sample and conjugate are incubated at room temperature for 1 hour before washing four times with 300 ul of wash buffer. 200 ul of substrate was then added followed by 0.1 M sulfuric acid 30 minutes later. The plates were then read on a spectrophotometer at 450 nm for calculations. DHEA-S was assayed as above for progesterone except only 50 ul of sample, 75 ul of conjugate, and 100 ul of substrate were used. For testosterone analysis, 50 ul of sample was added along with 50 ul of conjugate and 50 ul of antiserum. The samples were incubated for four hours, washed similarly to progesterone and 50 ul of substrate added prior to luminescence reading. For cortisol analysis, 50 ul of sample and conjugate was added prior to a 3-hour incubation, washing, the addition of 50 ul of substrate and instrument reading.

The study was conducted in accordance with several principles of research ethics, which included: ensuring the quality and integrity of the research; informed consent; respecting the confidentiality and anonymity of respondents; voluntary participation; avoiding harm; and that the research is independent and impartial.

2.1. End Points

The primary effectiveness end point in this study was the rate of change in hormone function from baseline at 30 and 60 days. Hormone levels were measured using a salivary hormone assay at baseline, 30 and 60 days. Secondary endpoints included assessments using a modified Cornell and Kupperman indices to evaluate symptoms associated with hormone imbalance and to identify any study related adverse events.

The primary safety end point of the trial was freedom from adverse events for 60 days. Since no adverse events were reported, review by a clinical events com-

mittee was not necessary.

2.2. Statistical Analysis

All analyses were on a per participant basis. A comparative analysis was done to detect a change from baseline, at 30 and at 60 days. A secondary analysis was completed to detect hormone stabilization at 60 days.

3. Results

Baseline demographic and clinical characteristics for the treatment group are summarized in Table 1. Baseline participant demographics and pre-treatment classification of symptoms (modified Cornell and Kupperman indices) were not significantly different between participants. In addition, preexisting risk factors were not different within participant groups. A total of 15 participants were treated using two metered, sublingual doses of spermine and spermidine three times per day for 30 days.

3.1. Cortisol

Glucocorticoids, primarily cortisol, are produced by the adrenal glands in response to stressors such as emotional upheaval, exercise, surgery, illness or starvation. In response to a stressor, most organisms have an automatic reaction that engages the mechanisms necessary for mobilization. This response, automatically activated as a defense against any threat, is designed to provide the energy resources necessary for survival and to shut down all unnecessary functions, such as digestive and reproductive functions. Consequently, in order for an organism to engage in sexual activity, the stress response would need to be inactive.

Cortisol plays an essential role in the stress response. Although there are a series of autonomic and endocrine responses that occur when an organism is faced with a stressor, cortisol has become commonly known as "the stress hormone". Cortisol's role in the endocrine system is metabolic, and it is released both after eating and in response to stressful situations. As part of the stress response, cortisol acts on various metabolic pathways to provide energy where it is needed in the body during a stressful fight or flight situation. Although increased cortisol release is not the only marker of the stress response, measuring cortisol response is a simple way to make a reasonable judgment about whether or not an organism is experiencing a stress response. This is particularly useful in sexual arousal

Table 1. Baseline patient characteristics.

	(n = 15)	Cortisol	DHEAS	Testosterone	Progesterone	Estradiol
Age, mean	37.1	7.1	6.8	48.9	30.3	2.2
Men	42.8	7.8	3.7	71.7	23.1	1.9
Women	32.2	6.8	7.5	29.0	36.5	2.0

Data are presented as mean (%) values, unless otherwise indicated.

studies because cortisol is only active in specific instances, whereas, for example, the sympathetic nervous system is activated in a variety of situations including both sexual arousal and during stress [15]-[21].

Cortisol is made from progesterone (Figure 1). In situations where there is excessive cortisol production and release in response to stress, progesterone levels decline. This happens because cortisol is much more necessary for life than progesterone, therefore progesterone gets converted into cortisol. Since cortisol and progesterone compete for common receptors in the cells, cortisol impairs progesterone activity, setting the stage for estrogen dominance. Without adequate progesterone, a fertilized egg will not be maintained in the uterus. According to the American Society for Reproductive Medicine, infertility affects about 10% of men and women of childbearing age. Chronically elevated cortisol levels can be a direct cause.

In this study, 83% of men and 37% of women experienced a significant reduction in cortisol during the 30-day supplementation with spermine and spermidine. Once the supplement was withdrawn the levels of cortisol began to rise among men but continued to decline among women, maintaining a50% mean decrease after an additional 30 days (Table 2, Table 3).

3.2. DHEAS

DHEA, or dihydroepiandrosterone, is one of the major steroid hormones produced by the adrenal glands, and sometimes by the gonads (ovaries and testes). The body converts DHEA into male and female sex hormones, such as estrogen and testosterone. When a sulfate group (special molecule containing a sulfur atom and four oxygen atoms), it forms DHEAS (dihydroepiandrosterone sulfate). Most DHEA is found as DHEAS in the blood. Women with infertility and men with erectile dysfunction frequently have low levels of DHEAS.

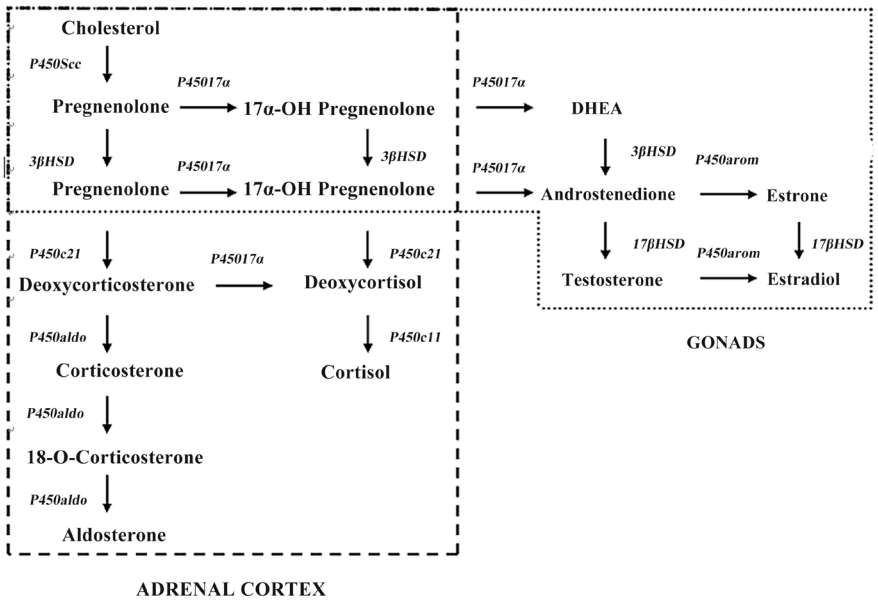

Figure 1. Hormone production diagram.

Table 2. Male cortisol levels.

Cortisol			30 days pg/mL	%	Dif 2/3 pg/mL	%	60 days pg/mL	%
Baseline	**Treatment**	**Post-Treatment**						
7.3	7.6	9.1	−0.3	4.1	−1.5	19.7	−1.8	24.7%
6.4	3.0	3.2	3.4	−53.1	−0.2	6.6	3.2	−50.0%
8.1	7.1	12.5	1.0	−12.3	−5.4	76.1	−4.4	54.3%
5.6	2.8	1.2	2.8	−50.0	1.6	−57.1	4.4	−78.6%
8.2	4.4	18.3	3.8	−46.3	−13.9	315.9	−10.1	123.1%
8.2	0.9	3.8	7.3	−89.0	−2.9	322.0	4.4	−53.7%
10.8	***	4.4	***	***	***	***	6.4	−59.3%
	Mean Decrease:		3.7 pg/mL	50%			4.6 pg/mL	60%

Table 3. Female cortisol levels.

Cortisol			30 days pg/mL	%	Dif 2/3 pg/mL	%	60 days pg/mL	%
Baseline	**Treatment**	**Post-Treatment**						
9.6	9.9	6.7	−0.3	3.1%	3.2	32.3%	2.9	30.2%
6.0	7.1	13.1	−1.1	18.3%	−6.0	84.5%	−7.1	118.3%
3.5	1.9	1.0	1.6	−45.7%	0.9	−47.4%	2.5	−71.4%
10.7	0.8	0.8	9.9	−92.5%	0.0	0.0%	9.9	−92.5%
7.9	8.9	9.1	−1.0	12.7%	−0.2	2.2%	−1.2	15.2%
6.1	2.3	1.8	3.8	−62.3%	0.5	−21.7%	4.3	−70.5%
2.0	4.3	3.4	−2.3	114.9%	0.9	−20.9%	−1.4	70.0%
6.1	8.4	14.0	−2.3	37.7%	−5.6	66.6%	−7.9	129.5%
	Mean Decrease:		5.1 pg/mL	66.8%			4.9 pg/mL	51.1%

In this study, 71% of men at 60 days and 87% of women at 30 days experienced a significant elevation in DHEAS following 30 day supplementation with spermine and spermidine (Table 4, Table 5).

3.3. Testosterone

Testosterone is the primary sex hormone in the male body. However, it is also present and needed in the female body for the same process, just in lesser quantities. Testosterone is responsible for the changes that come on around puberty in men such as the voice lowering, enlargement of the penis and testes and hair growth. It is also the key hormone behind the male libido, or the desire to have sex. In women, it is largely responsible for enhancing the female libido and sexual function. Testosterone can be made in three different places. For men, most of the testosterone is made in the testicles. For men and women, small amounts of testosterone can be made by the adrenal glands. For women only, small amounts can also be made in the ovaries.

Table 4. Male DHEAS levels.

DHEAS			30 days pg/mL	%	Dif 2/3 pg/mL	%	60 days pg/mL	%
Baseline	**Treatment**	**Post-Treatment**						
8.7	14.3	10.4	−5.6	64.4	3.9	−27.3	−1.7	19.5
42.2	3.9	9.8	38.3	−90.8	−5.9	151.3	32.4	−76.8
5.1	4.0	4.5	1.1	−21.6	−0.5	12.5	0.6	−11.8
10.1	5.9	4.5	4.2	−41.6	1.4	−23.7	5.6	−55.4
3.6	2.8	4.2	0.8	−22.2	−1.4	50.0	−0.6	16.7
6.9	1.5	5.3	5.4	−78.3	−3.8	253.3	1.6	−23.2
19.1	***	23.8	***	***	***	***	4.7	24.6
	Mean Increase:						8.9 pg/mL	38%

Table 5. Female DHEAS levels.

DHEAS			30 days pg/mL	%	Dif 2/3 pg/mL	%	60 days pg/mL	%
Baseline	**Treatment**	**Post-Treatment**						
4.4	5.5	7.2	−1.1	24.9%	−1.7	30.9%	−2.8	63.6%
12.2	13.0	9.5	−0.8	6.5%	3.5	−26.9%	2.7	−22.1%
1.3	1.4	0.7	−0.1	7.7%	0.7	−50.0%	0.6	−46.2%
5.2	2.8	3.5	2.4	−46.2%	−0.7	25.0%	1.7	−32.7%
6.7	7.5	8.8	−0.8	11.9%	−1.3	17.3%	−2.1	31.3%
7.6	8.8	5.6	−1.2	15.8%	3.2	−36.4%	2.0	−26.3%
9.5	20.7	12.5	−11.2	117.9%	8.2	−39.6%	−3.0	31.6%
13.2	16.2	11.1	−3.0	22.7%	5.1	−31.5%	2.1	−15.9%
	Mean Increase:		2.6 pg/mL	29.6%				

A testosterone production starts with signals that are transported from the pituitary gland and the hypothalamus. The hypothalamus produces a hormone called gonadotropin. This hormone transmits to the pituitary gland, which is then stimulated to produce follicle-stimulating hormones. These hormones run from the pituitary gland to the testicles and tell the testes to produce testosterone. The brain is then able to sense when the body has enough or too much testosterone and regulates its production through the pituitary gland.

Elevated cortisol associated with stress may cause a shortage of testosterone in the body. Not getting enough testosterone for men can mean a decreased sex drive and erectile dysfunction. In women, it can result in a lowered libido.

In this study, men under the age of 50 experienced a 48.9% testosterone increase in testosterone levels while women experienced a 48.8% increase in testosterone during the 30-day supplementation with spermine and spermidine (Table 6, Table 7).

3.4. Progesterone

Progesterone is secreted by the empty egg follicle after ovulation has occurred,

Table 6. Male testosterone levels.

Testosterone			30 days pg/mL	%	Dif 2/3 pg/mL	%	60 days pg/mL	%
Baseline	**Treatment**	**Post-Treatment**						
72.0	92.0	100.0	−20.0	27.7	8.0	8.7	28.0	38.8
55.0	52.0	101.0	3.0	−5.5	49.0	94.2	46.0	83.6
62.0	65.0	56.0	−3.0	4.8	9.0	−13.8	6.0	−9.7
75.0	50.0	35.0	25.0	−33.3	15.0	−30.0	40.0	−53.3
88.0	58.0	59.0	30.0	−34.1	−1.0	1.7	29.0	−32.9
105.0	31.0	52.0	74.0	−70.5	−21.0	67.7	53.0	−50.5
45.0	***	56.0	***	***	***	***	11.0	24.4
	Mean Increase:		11.5 pg/mL	16.3%			28.3 pg/mL	48.9%

Table 7. Female testosterone levels.

Testosterone			30 days pg/mL	%	Dif 2/3 pg/mL	%	60 days pg/mL	%
Baseline	**Treatment**	**Post-Treatment**						
34.0	39.0	31.0	−5.0	14.7%	8.0	−20.5%	3.0	−8.8%
26.0	40.0	34.0	−14.0	53.8%	6.0	−15.0%	−8.0	30.8%
18.0	27.0	13.0	−9.0	50.0%	14.0	−51.9%	5.0	−27.7%
36.0	16.0	12.0	20.0	−55.5%	4.0	−25.0%	24.0	−66.6%
31.0	38.0	39.0	−7.0	22.6%	−1.0	2.6%	−8.0	25.8%
46.0	39.0	22.0	7.0	−15.2%	17.0	−43.6%	24.0	−52.1%
17.0	35.0	21.0	−18.0	105.8%	14.0	−40.0%	−4.0	23.5%
24.0	35.0	35.0	−11.0	45.8%	0.0	0.0%	−11.0	45.8%
	Mean Increase:		10.6 pg/mL	48.8%				

known as the corpus luteum. It is highest during the last phases of the menstrual cycle, after ovulation. Progesterone causes the endometrium to secrete special proteins to prepare it for the implantation of a fertilized egg. When fertilization does not occur, it prevents the body from creating and releasing more eggs in the later stages of the menstrual cycle.

If conception has occurred, progesterone becomes the major hormone supporting pregnancy, with many important functions. It is responsible for the growth and maintenance of the endometrium. It also suppresses further maturation of eggs by preventing release of LH and FSH (Follicle Stimulating Hormone). By relaxing the major muscle of the uterus, progesterone prevents early contractions and birth. It does, however, also thicken the muscle helping the body prepare for the hard work of labor. Finally, progesterone suppresses prolactin (the primary hormone of milk production), preventing lactation until birth.

Progesterone is a female hormone used for reproduction but it is also found in

men. While progesterone still largely functions as a female reproduction facilitator, it can also be beneficial to men suffering from benign prostatic hyperplasia or an enlarged prostate. Men produce about half as much progesterone as women. They use it to make testosterone, the main male hormone, and produce cortisone, a hormone produced by the adrenal glands (Figure 1).

The prostate is a gland a little larger than a walnut that wraps around the urethra just under the bladder. It helps the fertilization process by producing a fluid filled with nutrients that mixes with the sperm to form semen and helps the sperm survive in the vagina's environment. The prostate experiences a growth spurt from male puberty to about the age of 20. It begins to grow again during a man's 40s as a natural part of aging. This is called benign prostatic hyperplasia and most men will have it by their 50s and 60s.

Men produce both testosterone and estrogen, another female hormone. The ratio of testosterone to estrogen is very high in a healthy man, but as men age that ratio can change. Many scientists believe that this is what causes the growth of the prostate as men age. Progesterone counteracts the effects of estrogen in men and improves the testosterone/estrogen ratios. It prevents testosterone from being converted into DHT, a weaker version of testosterone that dilutes the male hormone ratio.

In this study, 100% of men achieved an average decrease of 11.0 pg/mL (46.3%) in progesterone levels at 30 days and 85.7% maintained an average decrease of 10.0 pg/mL (37.2%) in progesterone levels at 60 days. One hundred percent of women with a decrease of progesterone levels at 30 days were either post-menopausal or in the luteal phase of the menstrual cycle. These levels remained lower than baseline at 60 days. On average progesterone levels decreased 22.8 pg/mL. However, 100% of women with an increase of progesterone levels at 30 days were in the follicular phase of menstruation. These levels remained higher than baseline at 60 days. On average, progesterone levels increased 32.0 pg/mL (Table 8, Table 9).

3.5. Estradiol

Estrogen is a group of hormones that are known best for their role in changing a girl into a woman with child-bearing potential. Estrogen also helps regulate the menstrual cycle, protects bones from thinning, and keeps cholesterol levels low to protect the heart. Estrogen can sometimes help turn normal breast tissue into cancers. Estrogen is made in three ways: within your body, in nature, and in a synthetic form used in medications. Estradiol is the form of estrogen produced by the ovary, and is what is measured during routine infertility monitoring.

Estrogen, like any other hormone, can be both beneficial and harmful. Research has shown that a few chemicals, called estrogenic xenobiotics, can mimic estrogen in the body and cause health problems the same way that excessive estrogen might do naturally. For example, the chemical nonylphenol, found in cleaning products, paints, herbicides, and pesticides, can damage human sperm.

Table 8. Male progesterone levels.

Progesterone			30 days pg/mL	%	Dif 2/3 pg/mL	%	60 days pg/mL	%
Baseline	**Treatment**	**Post-Treatment**						
22.0	18.0	13.0	4.0	−18.2	5.0	−27.7	9.0	−40.9
20.0	9.0	19.0	11.0	−55.0	10.0	111.1	1.0	−5.0
16.0	12.0	15.0	4.0	−25.0	3.0	25.0	1.0	−6.3
33.0	12.0	7.0	21.0	−63.6	5.0	−41.6	26.0	−78.8
21.0	5.0	26.0	16.0	−76.2	21.0	420.0	−5.0	23.8
25.0	15.0	15.0	10.0	−40.0	0.0	0.0	10.0	−40.0
25.0	***	12.0	***	***	***	***	13.0	−52.0
	Mean Decrease:		11.0 pg/mL	46.3%			10.0 pg/mL	37.2%

Table 9. Female progesterone levels.

Progesterone			Dif 1/2 pg/mL	%	Dif 2/3 pg/mL	%	Dif 1/3 pg/mL	%
Baseline	**Treatment**	**Post-Treatment**						
57.0	132.0	110.0	−75.0	131.6%	22.0	−16.6%	−53.0	92.9%
52.0	42.0	35.0	10.0	−19.2%	7.0	−16.6%	17.0	−32.7%
21.0	72.0	83.0	−51.0	242.9%	−11.0	15.3%	−62.0	295.2%
37.0	8.0	11.0	29.0	−78.4%	−3.0	37.5%	26.0	−70.3%
23.0	21.0	14.0	2.0	−8.7%	7.0	−33.3%	9.0	−39.1%
48.0	9.0	9.0	39.0	81.2%	0.0	0.0%	39.0	81.2%
38.0	49.0	44.0	−11.0	38.9%	5.0	−10.2%	−6.0	15.8%
16.0	16.0	23.0	0.0	0.0%	−7.0	43.8%	−7.0	43.8%
	Mean Decrease:		20.0 pg/mL				22.8 pg/mL	
	Mean Increase:		45.7 pg/mL	137.8%			32.0 pg/mL	111.9%

Many medicinal and edible plants contain compounds called phytoestrogens, which are chemically similar to the sex hormone estradiol, the primary estrogen in humans. Although it's generally regarded as a "woman's hormone", estradiol also occurs naturally in a man's body (it's produced in the testes). In addition, as in a woman's body, a man's body produces precursor hormones (including testosterone), which are converted to estradiol (Figure 1). In a man's body, estradiol is involved in sexual functioning, the synthesis of bone, cognitive functioning, and the modulation of several diseases (including cancer and heart disease).

In this study, 83% of men experienced a 55.9% decrease in estradiol in 30 days. This indicates that spermine and spermidine may be potent estrogen-blocking supplements. Fifty percent of women experienced a 36.8% increase in estradiol during the 30-day supplementation with spermine and spermidine, 75% of these also experiencing a concomitant increase in progesterone. Once the supplement was withdrawn the levels of estradiol began to decline among women and increase in men (Table 10, Table 11).

Table 10. Male estradiol levels.

Estradiol			30 days pg/mL	%	Dif 2/3 pg/mL	%	60 days pg/mL	%
Baseline	**Treatment**	**Post-Treatment**						
2.4	1.0	1.0	1.4	−58.3	0.0	0.0	1.4	−58.3
1.7	0.5	2.7	1.2	−70.6	2.2	440.0	−1.0	58.8
1.2	0.8	1.5	0.4	−33.3	0.7	87.5	−0.3	25.0
3.3	7.7	3.4	−4.4	133.3	4.3	−55.8	−0.1	3.0
1.2	0.5	0.8	0.7	−58.3	0.3	60.0	0.4	−33.3
1.7	0.7	1.8	1.0	−58.8	1.1	157.1	−0.1	5.9
1.6	***	1.5	***	***	***	***	0.1	−6.3
	Mean Decrease:		0.9 pg/mL	55.9%				
	Mean Increase:						0.4 pg/mL	32.6%

Table 11. Female estradiol levels.

Estradiol			30 days pg/mL	%	Dif 2/3 pg/mL	%	60 days pg/mL	%
Baseline	**Treatment**	**Post-Treatment**						
1.7	2.9	1.6	−1.2	70.6%	1.3	−44.8%	0.1	−5.8%
3.5	2.5	2.9	1.0	−28.6%	−0.4	15.9%	0.6	−17.1%
0.8	1.1	1.4	−0.3	37.5%	−0.3	27.3%	−0.6	74.9%
1.3	0.6	0.8	0.7	−53.8%	−0.2	33.3%	0.5	−38.5%
1.7	0.9	0.6	0.8	−47.0%	0.3	−33.3%	1.1	−64.7%
3.1	3.4	2.0	−0.3	9.7%	1.4	−41.2%	1.1	−35.5%
2.4	3.1	1.9	−0.7	29.2%	1.2	−38.7%	0.5	−20.8%
1.7	1.5	1.5	0.2	−11.8%	0.0	0.0%	0.2	−11.8%
	Mean Increase:		0.6 pg/mL	36.8%				
	Mean Decrease:						0.6 pg/mL	27.7%

3.6. Adverse Events

There were no adverse events reported or identified from the modified Cornell and Kupperman indices during the treatment phase of this trial or for 30 days post treatment.

4. Discussion

Spermine and spermidine, the biogenic polyamines found in food and produced endogenously from the amino acids ornithine and methionine, reduce cortisol levels in men and women, opening the way for improved sexual function and fertility. In this trial, supplementation with spermine and spermidine reduced cortisol levels by 58% in 30 days.

Further, elevated estradiol levels in men are associated with reduced sexual function and feminization (e.g. gynecomastia or breast enlargement). Most men

in this study experienced a 56% reduction in total salivary estradiol levels with 30 days of supplementation with spermine and spermidine. The decrease of estradiol in men potentially negates some of the loss of sexual function associated with estrogen dominance. A decreased level of estradiol in women is associated with reduced sexual function. Supplementation with spermine and spermidine increased estradiol levels in some women by 37% in 30 days and also improved the estrogen to progesterone ratio, again, potentially reducing the negative effects of estrogen dominance.

Increased testosterone levels are associated with improved sexual function in men and women. Testosterone levels increased in men under age 50 by 49% and increased DHEAS levels, both markers correlated with improved sexual function. Increased DHEA levels are associated with improved sexual function in men and women. DHEA was increased by 38% in 83% of men at 60 days and 88% in women in 30 days of supplementation.

For women, a decrease in progesterone levels has been associated with infertility, poor sexual function and rapid aging of the skin. In this study, 38% of women had an increase of progesterone levels at 30 days and 50% of women had an increase in progesterone levels at 60 days of supplementation. However, an increased progesterone level in men is associated with poor sexual function. After 30 days of supplementation with spermine and spermidine, 100% of men experienced a significant reduction (43%) in progesterone levels.

Women who experienced non-disabling mood swings and irritability associated with hormone fluctuations demonstrated a significant reduction in symptoms (80%) after only 30 days on spermine/spermidine supplementation. Further, women who experience low back and hip pain associated with hormone fluctuations demonstrated a significant reduction in symptoms (80%) after only 30 days on spermine/spermidine supplementation. Men likewise experienced reduction in pain or fatigue in the legs or back (62%).

Men experiencing low energy level or stamina realized a 50% improvement in symptoms and women experiencing unusual fatigue realized a 75% improvement in symptoms after only 30 days on spermine/spermidine supplementation.

Finally, among men experiencing a sense of bladder fullness and frequent or urgent need to urinate, 55% demonstrated a significant reduction in symptoms after only 30 days on spermine and spermidine supplementation. Women experiencing urinary difficulties found their symptoms were relieved (66%) after only 30 days on spermine/spermidine supplementation.

5. Conclusion

In this trial, treatment with spermine and spermidine supplementation was associated with a marked improvement in the stress response, sexual function, stamina, weight loss and a decrease in mood swings, irritability and fatigue when compared with non-treatment. The rate of improvement was significant within the thirty-day treatment period.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Groppa, M.D. and Benevides, M.P. (2008) Polyamines and Abiotic Stress: Recent Advances. Springer.

[2] Bardocz, S, Duguid, T.J., Brown, D.S., Grant, G., Pusztai, A., White, A., *et al.* (1995) The Importance of Dietary Polyamines in Cell Regeneration and Growth. *British Journal of Nutrition,* **73**, 819-828. https://doi.org/10.1079/BJN19950087

[3] Loser, C. (2000) Polyamines in Human and Animal Milk. *British Journal of Nutrition,* **84**, S55-S58. https://doi.org/10.1017/S0007114500002257

[4] Tabor, C.W. and Tabor, H. (1984) Polyamines. *Annual Review of Biochemistry*, **53**, 749-790. https://doi.org/10.1146/annurev.bi.53.070184.003533

[5] Loser, C. and Folsch, U.R. (1993) Importance of Various Intracellular Regulatory Mechanisms of Polyamine Metabolism in Camostate-Induced Pancreatic Growth in Rats. *Digestion*, **54**, 213-223. https://doi.org/10.1159/000201040

[6] Williams, H.G. and Lockwood, D.H. (1970) Role of Polyamines in Reproductive Physiology and Sex Hormone Action. Annals of the New York Academy of Science, Wiley Online Library.

[7] Loser, C., Eisel, A., Harms, D. and Folsch, U.R. (1999) Dietary Polyamines Are Essential Luminal Growth Factors for Small Intestinal and Colonic Mucosal Growth and Development. *Gut*, **44**, 12-16. https://doi.org/10.1136/gut.44.1.12

[8] Canellakis, Z.N., Marsh, L.L. and Bondy, P.K. (1989) Polyamines and Their Derivatives as Modulators in Growth and Differentiation. *Yale Journal of Biology and Medicine*, **62**, 481-491.

[9] Seidel, E.R. and Scemama, J.L. (1997) Gastrointestinal Polyamines and Regulation of Mucosal Growth and Function. *The Journal of Nutritional Biochemistry*, **8**, 104-111. https://doi.org/10.1016/S0955-2863(97)00025-9

[10] Kalac, P. and Krausova, P. (2004) A Review of Dietary Polyamines: Formation, Implications for Growth and Health and Occurrence in Foods. *Food Chemistry*, **90**, 219-230. https://doi.org/10.1016/j.foodchem.2004.03.044

[11] Dandrifosse, G., Peulen, O., El Khefif, N., Deloyer, P., Dandrifosse, A.C. and Grandfils, C. (2000) Are Milk Polyamines Preventive Agents against Food Allergy? *Proceedings of the Nutrition Society*, **59**, 81-86. https://doi.org/10.1017/S0029665100000100

[12] Dufour, C., Dandrifosse, G., Forget, P., Vermesse, F., Romain, N. and Lepoint, P. (1988) Spermine and Spermidine Induce Intestinal Maturation in the Rat. *Gastroenterology*, **95**, 112-116. https://doi.org/10.1016/0016-5085(88)90298-3

[13] Bardocz, S. (1995) Polyamines in Food and Their Consequences for Food Quality and Human Health. *Trends in Food Science & Technology*, **6**, 341-346. https://doi.org/10.1016/S0924-2244(00)89169-4

[14] Lovaas, E. and Carlin, G. (1991) Spermine: An Anti-Oxidant and Anti-Inflammatory Agent. *Free Radical Biology & Medicine*, **11**, 455-461. https://doi.org/10.1016/0891-5849(91)90061-7

[15] Exton, M.S., Bindert, A., Kruger, T., Scheller, F., Hartmann, U. and Schedlowki, M. (1999) Cardiovascular and Endocrine Alterations after Masturbation-Induced Or-

gasm in Women. *Psychosomatic Medicine*, **61**, 280-289. https://doi.org/10.1097/00006842-199905000-00005

[16] Exton, N.G., Truong, T.C., Exton, M.S., Wingenfeld, S.A., Leygraf, N., Saller, B., Hartmann, U. and Schedlowski, M. (2000) Neuroendocrine Response to Film-Induced Sexual Arousal in Men and Women. *Psychoneuroendocrinology*, **25**, 187-199. https://doi.org/10.1016/S0306-4530(99)00049-9

[17] Heiman, J.R., Rowland, D.L., Hatch, J.P. and Gladue, B.A. (1991) Psychophysiological and Endocrine Responses to Sexual Arousal in Women. *Archives of Sexual Behavior*, **20**, 171-186. https://doi.org/10.1007/BF01541942

[18] Sabater-Molina, M. and Zamora, S. (2007) Biological Significance of Dietary Polyamines. *Nutrition*, **23**, 87-95.

[19] Eliassen, K.A., Reistad, R., Risoen, U. and Ronning, H.F. (2002) Dietary Polyamines. *Food Chemistry*, **78**, 273-280. https://doi.org/10.1016/S0308-8146(01)00405-8

[20] Igarashi, K. and Kashiwagi, K. (2000) Polyamines: Mysterious Modulators of Cellular Functions. *Biochemical and Biophysical Research Communications*, **271**, 559-564. https://doi.org/10.1006/bbrc.2000.2601

[21] Deloyer, P., Peulen, O. and Dandrifosse, G. (2001) Dietary Polyamines and Non-Neoplastic Growth and Disease. *European Journal of Gastroenterology & Hepatology*, **13**, 1027-1032. https://doi.org/10.1097/00042737-200109000-00005