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Preliminary Hormonal Correlations in Female Patients as a Function of Somatic and Neurological Symptom Clusters: An Exploratory Development of a Multi-Hormonal Map for Bio-Identical Replacement Therapy (MHRT)

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Abstract

Females develop multiple hormonal alterations and certain genes may be involved in the intensity of subsequent symptoms including both mood and drug seeking. Seventy Four (74) females were included (mean age=60.23, SD=9.21, [43-87]). A medical evaluation was completed with hormone screening using a number of statistical analyses such as Pearson product moment; one way ANOVA and Regression analysis along with a Bonferroni significance correction p<.004. Of 120 correlations performed, significant hormone/domain correlations were as follows: DHEA/Genitourinary (r=.30, p<.05); FSH/Pulmonary (r=-.29, p<.05); Pregnenolone/Genitourinary (r=.40, p<.006) /Immunological (r=.38, p<.008); Testosterone/total endorsed symptoms (r=-0.34, p<.016); TSH/Pulmonary (r=-.33, p<.03) /Gynecological (r=.30, p<.05). Estrone/Musculoskeletal (r=-0.43, p<.012). After a Bonferroni correction (experiment-wise p<.00045) for statistical significance, no hormones remained significance. In the follow–up phase FSH/Neuropsychiatric (r=.56, p<.05) and Musculoskeletal (r=.67, p<.013); DHEA/Immunological (r=.64, p<.04); LH/ Musculoskeletal (r=.59, p<.34); Free Testosterone/Neuropsychiatric (r=.64, p<.019), Musculoskeletal (r=.68, p<.01), and Dermatologic (r=.57, p<.04); Total Testosterone/Immunological (r=.63, p<.028); TSH/Endocrinological (r=-.62, p<.031). Factor analysis of the MQ yielded two factors with eigenvalues > 1.0 (high loadings: first: Pulmonary, GI, Cardiovascular, and Immunological; second: Musculoskeletal, Gynecological, and the three Neurological domains). Both factors had significant correlations: first/pregnenolone (r=.37, p<.019); second/TSH (r=.33, p<.034). An additional factor analysis of hormone level clusters showed significant correlations with various domains. This study highlights the need to test the core biological endocrine hormones associated with females. Future research will focus on the relationship of for example Leptin and the electrophysiology of the brain. We are cautiously proposing a new paradigm shift whereby we replace the old nomenclature of HRT to MHRT.

Keywords: Female aging; Hormones; Women's health; Two-factor analysis; HRT

Introduction

Many women become deficient in multiple hormones such as estrogen, progesterone, testosterone, and DHEA with increases in LH, Follicle Stimulating Hormone (FSH) and Thyroid Stimulating Hormone (TSH) as they age [1-10]. All of these hormones have individual as well as inter-related functions in the human body, including pulmonary, cardiovascular, GI and immunological functions. As increased life expectancy has changed the aging pyramid, clinical attention increasingly focuses on an identified decline in cognitive function due to the normal aging process [6,11]. In fact, estrogen deficiency has been proposed as a cause of memory deficits in postmenopausal women [12]. There are studies which suggest that LH increases after menopause with concomitant decline in cognitive performance [13]. Chorionic gonadotropin receptors and LH occur in the brain [14]. Thus, levels of LH and FSH may increase low-density lipoprotein receptor–related protein in the brain [12,15]. Levels of FSH increase dramatically in women during and after menopause and can be lowered with estrogen therapy [12,16]. Emerging evidence suggests that high TSH levels are associated with a two-fold risk of cognitive decline as well as prevalence of anomalies in musculoskeletal systems [17-19].

We hypothesized that females (mean age=60.23, SD=9.21, [43-87]) presenting at a primary care clinic in New York City would have a number of associated hormonal changes relating specifically to both somatic and neurological symptoms. We used various statistical methods to examine the relationship of hormone levels and symptom complexes, including Pearson Product-Moment correlations, factor analysis, and ANOVA.

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Materials and Methods

Subjects

All female patients, who presented to a private clinic, at or approaching the typical age of menopause or post menopause onset were examined. A total of 74 women were entered into the study, although every woman did not have all variables available for analysis. The mean age of the sample was 60.23 (SD = 9.21, range = [43-87]). Thus most patients were post-menopause. Medical history, physical examination and laboratory analysis determined that 37 patients had uncomplicated age-related menopause, 11 had menopause related to gynecological surgery, 4 had gynecological organ disease without surgery, and 22 had menopause of ambiguous origin. Each patient filled out an approved IRB PATH informed consent and the IRB committee approved the study on May 20, 2009 [Registration # IRB00002334, Protocol #: LEXMEN001].

Design

All subjects underwent a thorough medical evaluation including a full screen for hormones including DHEA sulfate, estradiol, estrone, FSH, LH, pregnenolone, progesterone, free and total testosterone, and TSH obtained from an outside laboratory. A detailed medical history was obtained including information on the stage of menopause (not yet, undergoing, or through), origin of the menopause, and history of HRT. A Menopause Questionnaire (MQ) was given to all women (n=74) independent of age, following a preliminary screening (Figure 1). The quantitative section of the MQ consisted of 64 questions related to symptoms of menopause. Each symptom was rated on a Likert scale of frequency from 1 (never) to 5 (always). The total number of endorsed symptoms was calculated as a gross indicator of menopausal symptomotology. Mean values of the Likert ratings were also calculated within each of 12 domains of symptoms: Neurological, Neuropsychiatric, Neuropsychological, Endocrine, Pulmonary, Musculoskeletal, Gastrointestinal, Cardiovascular, Dermatological, Genitourinary, Immune, and Gynecological. A grand mean of the Likert rating across all domains was also calculated. Patients were mailed a follow-up MQ 6 months after their initial assessment.

Analyses

Pearson product-moment correlations were calculated between hormone levels and the 12 mean domain scores, the total number of endorsed systems, and the grand mean across all 64 questions of the MQ. A one-way analysis of variance was performed for the origin of menopause variable for each of the 12 symptom domains, with a Bonferroni correction of p<.004 required for significance. Given the large number of domains and likely high inter-correlations between them, a factor analysis with principal components extraction and varimax rotation was performed on the 12 mean domain scores. Factor scores were generated for each patient and entered into the correlation analysis with the hormone levels. A similar factor analysis was performed on the hormone levels to reduce redundancy of highly inter-correlated values. Regression analyses were performed to predict the symptom domain score factors from the 10 hormone levels and again using the hormone level factors. Similar analyses were performed on the follow-up MQ's, but there were only 13 patients with follow-up data available. We have attempted to increase this number but were unsuccessful.

Results

Pearson product-moment correlations

Age did not correlate significantly with any of the hormone levels, symptom domains, total endorsed symptoms, or grand MQ mean. Significant correlations between hormone levels and the 12 MQ symptom domains appear in Table 1. DHEA correlated significantly with the Genitourinary domain (r=.30, p<.05). Estrone had a negative correlation with the Musculoskeletal domain (r=-0.43, p<.012). FSH correlated significantly with the Pulmonary domain (r=-.29, p<.05). Pregnenolone correlated significantly with the Genitourinary (r=.40, p<.006) and Immunological (r=.38, p<.008) domains. Testosterone correlated significantly with the total number of symptoms endorsed (r=-.34, p<.016) but with none of the 12 MQ symptom domains. TSH correlated significantly with the Pulmonary (r=-.33, p<.03) and Gynecological (r=-.39, p<.03) domains (Figure 2).

However, given the large number (120) of correlations performed between hormone and symptom variables, a Bonferroni correction was applied with an experiment-wise significance level of p<.00045 required for interpretation of statistical significance. None of the hormones remained significantly correlated with a symptom domain after the Bonferroni correction (Table 1).

Significant correlations between hormone levels and follow-up MQ symptom domains appear in Table 2. DHEA correlated significantly with the Immunological domain (r=.65, p<.04). FSH correlated significantly with the Neuropsychiatric (r=.56 p<.05) and Musculoskeletal (r=.67, p<.013) domains. LH correlated significantly with the Musculoskeletal domain (r=.59, p<.034). Free testosterone correlated significantly with the Neuropsychiatric (r=.64, p<.019), Musculoskeletal (r=.68, p<.01) and Dermatologic (r=.57, p<.04) domains, and total testosterone correlated significantly with the Immunological domain (r=.63, p<.028) Finally, TSH correlated negatively (r=-.62, p<.031) with the Endocrinological domain (Figure 3).

However, none of these correlations was significant after applying the Bonferroni correction for multiple comparisons, requiring p<.00045 (Table 2).

Factor analysis

A factor analysis of the MQ yielded two factors with Eigen values > 1.0. The first factor had high loadings from the Pulmonary, GI, Cardiolovascular, and Immunological domains. The second factor had high loadings from all three neurologically related domains as well as the Musculoskeletal and Gynecological domains. The first factor correlated significantly with pregnenolone (r=.37, p<.019) and the second factor correlated significantly with TSH (r=.33, p<.034) (Figure 4).

A factor analysis of the hormone levels yielded 4 factors. Factor 1 had high loadings from DHEA, Progesterone, Free Testosterone, and Testosterone Total. Factor 2 had high loadings from FSH and LH. Factor 3 had high loadings from Estrone and Progesterone. The fourth factor had high loadings from Pregnenolone and TSH. Factor 1 did not correlate with any of the symptom domains or with the symptom factors. Factor 2 correlated significantly with the Endocrinological domain (r=-.47, p<.012). Factor 3 correlated significantly with the Pulmonary (r=-.43, p<.035), Musculoskeletal (r=-.43, p<.024), and Genitourinary (r=-.49, p<.009) domains (Figure 5).

MENOPAUSE QUESTIONNAIRE

NAME: ____________________ **DATE OF BIRTH:** _____ **AGE:** _____**Today's Date** _____

NOTE: This research is not limited to women currently experiencing menopause. *All information disclosed here is solely for research purposes conducted by the PATH Research Foundation.*

1) What is your current menopausal status?

1) Not yet at menopause 2) Undergoing menopause 3)Through menopause

2) How long (in months or years) have you been in menopause? ________________

3) Was your menopause:

1) Natural and age-related
2) Not age-related due to (please circle all that apply):
A) Surgery B) Disease/injury C) Premature ovarian failure D) Chemotherapy/radiation/medication

4) Have you had any of these operations?

1) Hysterectomy (uterus removal)
2) Oophorectomy (ovary removal): A) One ovary B) Both ovaries
3) None of the above

5) Are you currently using Hormone Replacement Therapy (HRT)?

1) No—I have never taken prescription HRT
2) No—I have taken HRT but I am currently not. **If so, how long ago did you stop using hormones?** _____
3) Yes—estrogen only
4) Yes—progesterone only
5) Yes—estrogen and progesterone
6) Yes—estrogen and other hormones

6) Are you taking any medications that affect your hormone levels? (If yes, please list them)

____

7) How long have you been at PATH Medical for treatment? ________________

8) Please note if you have or have had any of the following conditions or diseases. If any of these conditions have increased in severity, please make a note in the margins, where applicable.

1) Diabetes
2) Problems with thyroid, parathyroid, adrenal glands
3) Respiratory disease
4) Osteoporosis
5) Coronary artery disease
6) Hyperlipidemia (high blood levels of lipids, including cholesterol)
7) Breast cancer
8) Ovarian cancer
9) Uterine cancer
10) Any other form of cancer? If yes, please state: _____________

9) Have you gained or lost any weight within the past:

1) GAINED/LOST: Three years? YES/NO If yes, how much? _________
2) GAINED/LOST: Five years? YES/NO If yes, how much? _________
3) GAINED/LOST: Ten years? YES/NO If yes, how much? _________

10) How often do you exercise?

1) Rarely 2) 1-3 times a week 3) 4-7 times a week

HOW OFTEN DO YOU EXPERIENCE THE FOLLOWING SYMPTOMS?

NEVER	RARELY	SOMETIMES	OFTEN	ALWAYS
1	2	3	4	5

NEUROLOGICAL
Tingling in hands and feet
Dizzy spells
Loss of appetite
Loss of desire (to be active or do work)
Headaches/Ringing in ears

NEUROPSYCHIATRIC
Nervous tension
Dry nose and mouth
Difficulty concentrating
Depression
Anxiety
Memory loss

NEUROPSYCHOLOGICAL
Lack of energy/Fatigue

Feeling sad/downhearted; tearfulness
Difficulty sleeping
Irritability/Agitation
Panic
Mood swings

ENDOCRINE:
Hot flashes
Night sweats
Dry/itchy eyes

PULMONARY:
Increased asthma
Persistent cough

MUSCULOSKELETAL:
Joint pain or stiffness
Backache
Muscle tension

GASTROINTESTINAL:
Diarrhea
Constipation
Irritable bowel syndrome
Increased reflux (heartburn)
Increased gas
Bloating
Increased indigestion
Increased nausea

CARDIOVASCULAR:
Swelling
Chest pain on exertion
Shortness of breath on exertion
Rapid/irregular heartbeat

Cold sweats

DERMATOLOGICAL:
Skin rash/irritation
Dry skin
Thinning skin
Hair loss or thinning- head, pubic area, anywhere on body
Increase in facial hair
Changes in fingernails: softer, crack or break easier
Increased acne

GENITOURINARY:
Discomfort passing urine
Inability to control urine, especially upon sneezing, laughing
Overactive bladder—frequent, sudden urges to urinate
Bladder infection
Leakage of feces
Incidence of urinary tract infections

IMMUNE:
Increased cysts
Sore throat
Allergies
Gum problems, increased bleeding

GYNECOLOGICAL:
Breast soreness
Breast pain
Vaginal discharge
Dry vagina
Irritation of the tissues in and around the vagina

Pain in vaginal area (including during sexual intercourse)
Loss of sex drive
Decreased sexual response
Irregular periods
# of sexual events per week : _______________

Figure 1: Menopause Questionnaire assessing MHRT treatment and severity of symptoms.

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Hormone	Symptom Domain	r	P	Hormone Change
DHEA	Genitourinary	0.30	<0.05	Increase
Estrone	Musculoskeletal	-0.43	<0.012	Decrease
FSH	Pulmonary	-0.29	<0.05	Decrease
Pregnenalone	Genitourinary	0.40	<0.006	Increase
	Immunological	0.38	<0.008	Increase
Testosterone	all symptoms	-0.34	<0.016	Decrease
TSH	Pulmonary	-0.33	<0.03	Decrease
	Gynecological	-0.30	<0.03	Decrease

*Note all symptoms include genitourinary, musculoskeletal, immunological, pulmonary, and gynecological

Table 1: Significant Correlations of Hormones with MQ Symptom Domains.

ANOVA and regression analysis

The one-way ANOVAs on the MQ symptom domains and the two MQ factors between the origin of menopause (age-related, surgery, disease) were not significant. The one-way ANOVAs on the MQ symptom domains and the two MQ factors between the younger (40-59) and older (≥ 60) subjects were not significant. A stepwise regression analysis to predict symptom domain factors from the 10 hormone levels was not significant. Similarly, a stepwise regression analysis to predict symptom domain factors from the four hormone level factors was not significant.

Discussion

Our data show significant correlations with menopause symptomotology in those patients within the menopause age range (39-59) derived from a total cohort of females ranging in age from 43 to 87 years, prior to taking estrogen. These hormonal correlations include DHEA associated with Genitourinary; testosterone with all symptoms; FSH with Pulmonary; TSH with both Pulmonary and Gynecological; Estrone with Musculoskeletal; and Pregnenolone with both Immunological and Genitourinary. While we attempted to obtain data on a follow-up questionnaire only 13 patients responded following a mailed survey. Although this provided us with a small number for subsequent statistical analysis we did find significant correlations with FSH and Immunological and Dermatological symptoms as well as Pregnenolone with Immunological symptoms in this population. When we utilized a Bonferroni correction for multiple comparisons, none of these correlations were significant except for TSH, which correlated at r = .52 ($p<.0001$) with the Pulmonary domain. We are confident that the significant correlations have clinical relevance because the Bonferroni correction was at a very conservative level at $p< 0.0045$.

Most interestingly, our results using factor analysis identified important symptom clusters with both somatic and neurological associations. In terms of the somatic symptoms pregnenalone was significantly associated at the $p< 0.019$ level (Figure 1). Our finding related to TSH correlating significantly with both neurological and musculoskeletal symptoms is in agreement with the work of Cakir et al. [20]. They demonstrated that musculoskeletal disorders often accompany thyroid dysfunction. In addition to the well–known observation that these disorders are common in patients with hypothyroidism, they are also observed in patients with thyrotoxicosis. The fact that we found an increase in TSH levels during menopause patients (not older) may be evident of a defensive mechanism by which the body is attempting to protect the menopausal female from aches and pains associated with musculoskeletal complaints. Moreover, during menopause high levels of TSH are related to vasomotor complaints [21]. In addition, our finding of increased levels of LH and its association with the neuropsychiatric symptom cluster is in agreement with the work of Bowen et al., showing that elevated LH expression co-localizers with neurons vulnerable to Alzheimer's disease pathology

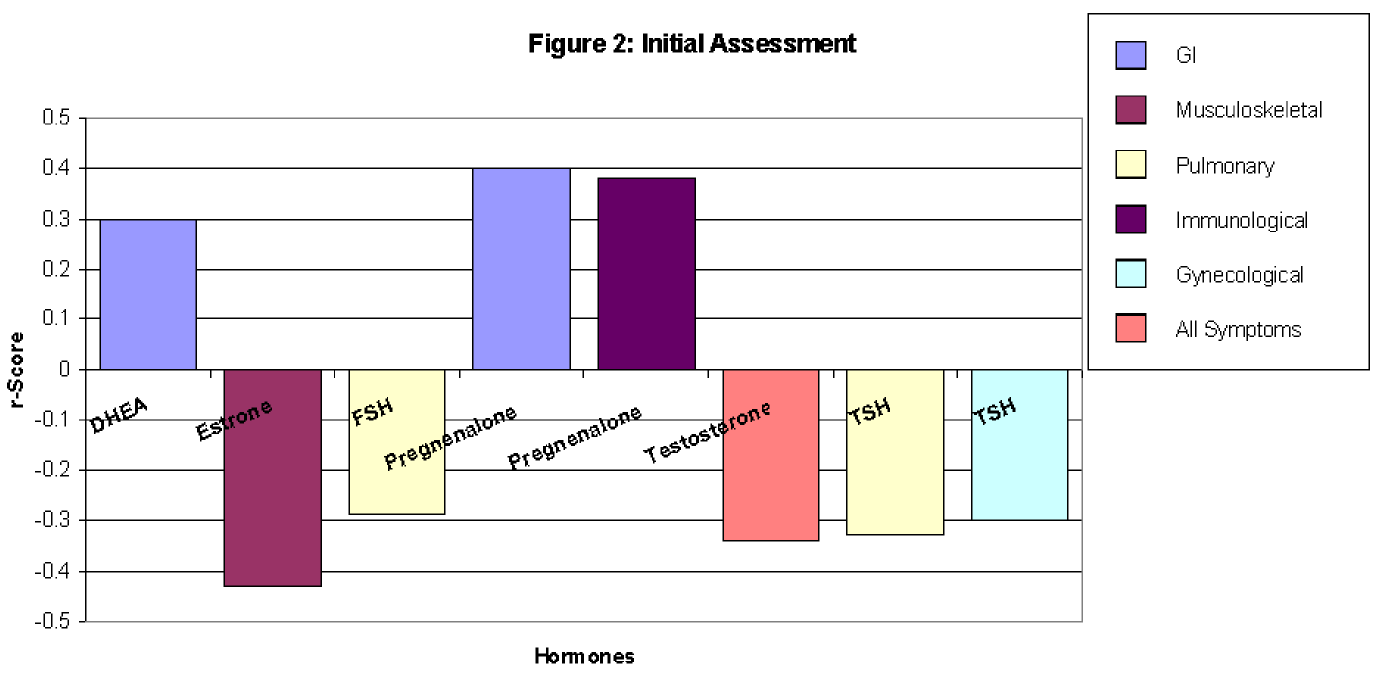


Figure 2: Initial Assessment found significant correlations between DHEA and Genitourinary domain, FSH and Pulmonary domain, Pregnenolone and Genitourinary domain, Pregnenolone and Immunological domain, Testosterone and the total number of symptoms, TSH and Pulmonary domain, and TSH and Gynecological domain. Negative correlations were found between Estrone and Musculoskeletal domain and Estrone and Immunological domain.

Hormone	Symptom Domain Correlation(s)	Value, r	Value, p	Hormone Change
TSH	Endocrinological	-0.62	<.031	Decrease
LH	Musculoskeletal	0.59	<.34	Increase
FSH	Neuropsychiatric	0.56	<.05	Increase
	Musculoskeletal	0.67	<.013	Increase
DHEA	Immunological	0.64	<.04	Increase
Free Testosterone	Neuropsychiatric	0.64	<.019	Increase
	Musculoskeletal	0.68	<.01	Increase
	Dermatologic	0.57	<.04	Increase
Total Testosterone	Immunological	0.63	<.028	Increase

Table 2: Follow-up Assessment.

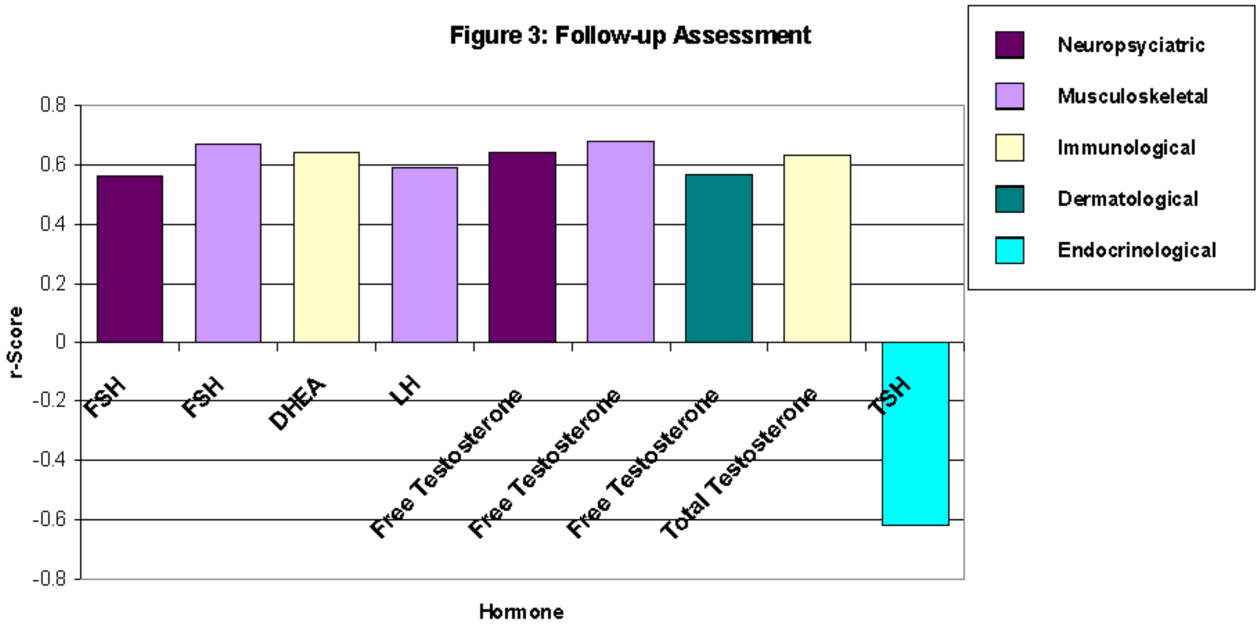


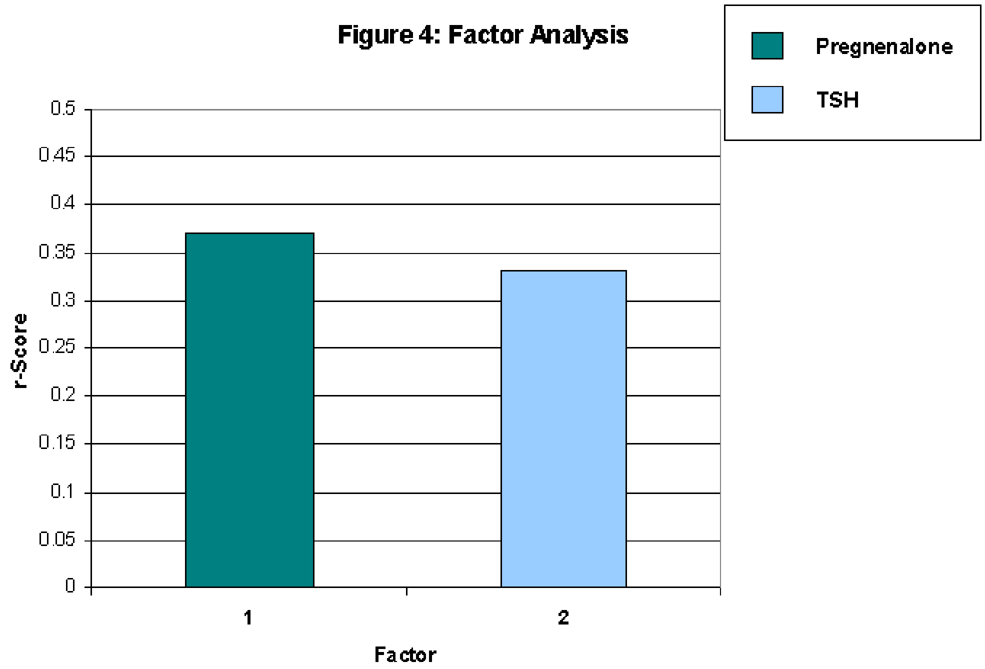
Figure 3: Follow-up Assessment found significant correlations between DHEA and Immunological domain, FSH and Neuropsychiatric domain, FSH and Musculoskeletal domain, LH and Musculoskeletal domain, Free testosterone and Neuropsychiatric domain, Free testosterone and Musculoskeletal domain, Free testosterone and Dermatologic domain, and total testosterone and Immunological domain. Negative correlation was found between TSH and Endocrinological domain.

[22]. LH agonists are known to affect three primary sites within the skeletal muscle, namely androgen receptors, the neuromuscular junction, and the second messenger systems, which includes insulin-like growth factor-1. All sites have been demonstrated to lead to a decrease in isokinetic exercise strength in large muscle groups [23]. The clustering of FSH with the musculoskeletal domain is not surprising since it has been shown that FSH levels increase during isokinetic resistance to exercise [24]. Our finding of DHEA association with the immunological symptom cluster is in agreement with the recent review of Hazeldine et al. which correctly pointed out that DHEA secretion declines with age, a phenomenon referred to as the "adrenopause" [25]. There are now many studies suggesting that DHEA plays a role in regulating human immunity, concurring with our factor analysis data.

In agreement with our factor analysis, increased serum free testosterone concentration predicts memory performance and cognitive status in the elderly [26]. Elevated free testosterone levels in women are associated with acne [27]. This is in agreement with our finding that free testosterone is associated with the dermatologic symptom cluster. Finally, it is well established that total testosterone is responsible for depressing macrophage immune function after soft tissue hemorrhagic shock, a finding related to human regulation of immunity [28].

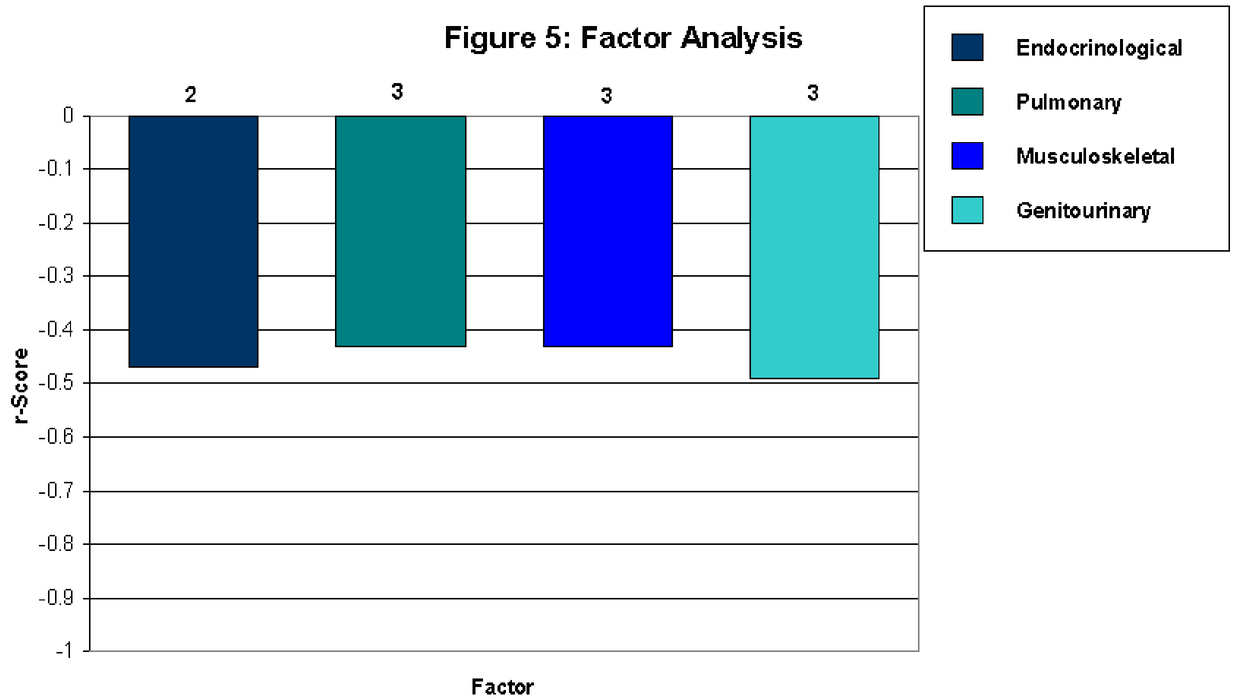
It is noteworthy that ovarian activity is controlled by a "biological clock" in the hypothalamus. This controls the pituitary by a gonadotropin-releasing hormone. In response the pituitary secretes FSH and LH. Subsequently, the corpus luteum is created in the ovary, secreting progesterone while estrogen secretion continues. A cyclic drop in pituitary gonadotropin secretions causes the corpus luteum to degenerate. The ovary makes estrogen from cholesterol by converting it first to pregnenolone, then to progesterone, then to androstenedione and finally to estradiol. Estradiol is the estrogen secreted by the ovary, but it can be changed in the liver to estrone and estriol. The pathways of the steroid hormone synthesis are the same in the adrenal cortex. Furthermore, when estrogen deficiency occurs in menopause, LH levels increase. Later FSH rises and remains elevated for the rest of life. These raised FSH and low estrogen levels appear to be the causes of the characteristic hot flashes. Abrupt deprivation of estrogen causes more symptoms than a slow decline of function. Estrogen therapy may relieve these symptoms but not without adverse effects [29].

Since the adjustment of tissues to an altered hormonal environment



Factor 1: Cluster of Pulmonary, GI, Cardiovascular, and Immunological domains
Factor 2: Cluster of Musculoskeletal, Gynecological, and all 3 Neurological domains

Figure 4: Factor Analysis yielded two factors. First factor had high loadings from the Pulmonary, GI, Cardiovascular, and Immunological domains. Second factor had high loadings from all three neurological domains as well as Musculoskeletal and Gynecological domains.



Factor 2: Cluster of FSH and LH
Factor 3: Cluster of Estrone and Progesterone

Figure 5: Factor Analysis yielded 4 factors. Factor 1 had high loadings from DHEA, Progesterone, Free Testosterone, and Testosterone Total. Factor 2 had high loadings from FSH and LH. Factor 3 had high loadings from Estrone and Progesterone. Factor 4 had high loadings from Pregnenolone and TSH.

as a function of age may have impacted our findings, we decided to adjust for age as a co-variate. However, when we adjusted for age as a co-variate, we did not find any other significant differences. In follow-up research we will also access hormonal changes as a function of aging according to decades as a comparative analysis between premenopausal and postmenopausal females. We are also investigating the relationship of hormonal correlates in menopausal women (age range 40-59) with the electrophysiology of the brain. Specifically the association of not only sex hormones but leptin and both voltage and latency (speed) of P300. In follow-up research we will also assess hormonal changes as a function of aging according to decades as a comparative analysis between pre menopausal and post menopausal females.

While our results are encouraging, we hope that larger studies will confirm these interesting findings. We believe that continued research in this area will ultimately provide a hormonal map which will inform the clinician as to what other specific hormones should be targeted besides estrogen. In fact, Mahmud has already suggested a multi-hormonal replacement approach using natural bio-identical products [1]. By utilizing the factor analysis approach we are beginning to develop a number of hormonal clusters that map to menopause and will ultimately serve as a basis for our newly proposed bio-identical Multi-Hormone Replacement Therapy (MHRT).

While this study highlights the importance of attempting to correlate certain hormonal changes with aging in females there are many studies showing the role of genetics in the intensity and age of onset in menopause. This suggests that certain polymorphisms including those related to hormones may reflect inheritable associations. For example, Genome-Wide Association Studies (GWAS) have been successful in uncovering genetic determinants of age at menarche and age at natural menopause [30]. It is noteworthy, that more than 30 novel genetic loci have been identified in GWAS for age at menarche and 17 for age at natural menopause. However, the genetic loci identified so far account for only a small fraction of the overall heritability and more research is encouraged.

Conclusion

We have determined a number of important significant correlations with multiple hormone alterations associated with aging females. Most interestingly, aging female patients suffer from both somatic and neurological deficits, which we have now found to be significantly associated with certain hormonal correlates, specifically pregnenolone with a somatic cluster and TSH with a neurological and musculoskeletal cluster, which agrees with the current literature.

Moreover, aging-induced hormonal changes and symptoms in medicine in general are multifactorial, depending on each person's biological and genetic makeup. It is not surprising that one set hormonal pattern is unable to predict any particular cluster of menopausal symptoms. Instead, multiple hormones have been related to numerous clusters of menopausal symptoms in patients (age 39-59) that have multiple endocrine abnormalities. This study highlights the need to test the core biological endocrine hormones associated with aging, and to establish a standard in evaluating female aging from a multi-hormonal perspective. We cautiously following required research, propose a new paradigm shift whereby we replace the old nomenclature of HRT to MHRT.

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