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)

Eric R Braverman1,2, Marlene Oscar-Berman3, Florian Kreuk1, Mallory Kerner1, Kristina Dushaj1, Mona Li1, Danielle Stratton1, Courtney Trudesdell1, and Kenneth Blum1,2,4,5,*

1Department of Clinical Neurology, PATH Foundation NY, New York, United States of America
2Department of Psychiatry, University of Florida, College of Medicine and McKnight Brain Institute, Gainesville, Florida, United States of America
3Departments of Psychiatry and Anatomy and Neurobiology, Boston University School of Medicine and Boston VA Healthcare System, Boston, Massachusetts, United States of America
4Department of Psychiatry, Human Integrated Services Unit, University of Vermont, Center for Clinical and Translational Science, Burlington, Vermont, United States of America
5Institute of Integrative Omics & Applied Biotechnology, Nonakuri, Purba Medinipur, West Bengal, India

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

Copyright: © 2013 Braverman ER, et al.
This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

*Corresponding author: Department of Psychiatry, University of Florida, College of Medicine and McKnight Brain Institute, Gainesville, Florida. Tel: 619-890-2167, drd2gene@gmail.com.
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.

**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 symptomatology. 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 ($r=−.43, p<.012$). 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).
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 symptomatology 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 [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 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.

Acknowledgments

The authors appreciate the expert edits made by Margaret A. Madigan. The preparation and review of the manuscript was supported in part by funds from the National Institutes of Health, NIAAA (R01-AA07112 and K05-AA00219) and the Medical Research Service of the US Department of Veterans Affairs (Marlene-Oscar-Berman). Dr. Kenneth Blum and Eric R. Braverman are the recipients of a grant from Life Extension Foundation, Ft. Lauderdale, Florida.

Source of funding This work has been generously funded by a grant from the Life Extension Foundation located in Fort Lauderdale, Florida.

References

1. Mahmud K. Natural hormone therapy for menopause. Gynecol Endocrinol. 2010; 26:81–85. [PubMed: 19995152]
2. Diamanti-Kandarakis E, Lambrinoudaki I, Economou F, Christou M, Piperi C, et al. Androgens associated with advanced glycation end-products in postmenopausal women. Menopause. 2010; 17:1182–1187. [PubMed: 20647960]
3. O’Connor KA, Ferrell R, Brindle E, Trumble B, Shofer J, et al. Progesterone and ovulation across stages of the transition to menopause. Menopause. 2009; 16:1178–1187. [PubMed: 19568209]
4. Panay N, Al-Azzawi F, Bouchard C, Davis SR, Eden J, et al. Testosterone treatment of HSDD in naturally menopausal women: the ADORE study. Climacteric. 2010; 13:121–131. [PubMed: 20166859]
5. Berent-Spillson A, Persad CC, Love T, Tkaczyk A, Wang H, et al. Early menopausal hormone use influences brain regions used for visual working memory. Menopause. 2010; 17:692–699. [PubMed: 20300040]
6. Newhouse PA, Dumas J, Wilkins H, Coderre E, Sites CK, et al. Estrogen treatment improves cognitive performance after psychosocial stress and monoamine depletion in postmenopausal women. Menopause. 2010; 17:860–873. [PubMed: 20616673]
7. Lord C, Engert V, Lupien SJ, Pruessner JC. Effect of sex and estrogen therapy on the aging brain: a voxel-based morphometry study. Menopause. 2010; 17:846–851. [PubMed: 20616671]
8. Wiacek M, Hagner W, Zubrzycki IZ. Measures of menopause driven differences in levels of blood lipids, follicle-stimulating hormone, and luteinizing hormone in women aged 35 to 60 years: National Health and Nutrition Examination Survey III and National Health and Nutrition Examination Survey 1999-2002 study. Menopause. 2010; 18:1–7.
9. Bryan KJ, Mudd JC, Richardson SL, Chang J, Lee HG, et al. Down-regulation of serum gonadotropins is as effective as estrogen replacement at improving menopause-associated cognitive deficits. J Neurochem. 2010; 112:870–881. [PubMed: 19943850]
10. Kåss AS, Lea TE, Torjesen PA, Gulseth HC, Førre ØT. The association of luteinizing hormone and follicle-stimulating hormone with cytokines and markers of disease activity in rheumatoid arthritis: a case-control study. Scand J Rheumatol. 2010; 39:109–117. [PubMed: 20337546]
11. Anderer P, Saletu B, Gruber D, Linzmayer L, Semlitsch HV, et al. Age-related cognitive decline in the menopause: effects of hormone replacement therapy on cognitive event-related potentials. Maturitas. 2005; 51:254–269. [PubMed: 15978969]
12. Gibbs RB. Estrogen therapy and cognition: a review of the cholinergic hypothesis. Endocr Rev. 2010; 31:224–253. [PubMed: 20019127]
13. Short RA, Bowen RL, O’Brien PC, Graff-Radford NR. Elevated gonadotropin levels in patients with Alzheimer disease. Mayo Clin Proc. 2001; 76:906–909. [PubMed: 11560301]
14. al-Hader AA, Tao YX, Lei ZM, Rao CV. Fetal rat brains contain luteinizing hormone/human chorionic gonadotropin receptors. Early Pregnancy. 1997; 3:323–329. [PubMed: 10086084]
15. Wich BK, Carnes M. Menopause and the aging female reproductive system. Endocrinol Metab Clin North Am. 1995; 24:273–295. [PubMed: 7656892]
16. Foster JD, Strauss JF 3rd, Paavola LG. Cellular events involved in hormonal control of receptor-mediated endocytosis: regulation occurs at multiple sites in the low density lipoprotein pathway, including steps beyond the receptor. Endocrinology. 1993; 132:337–350. [PubMed: 8419131]
17. Davis JD, Pedolanczuk A, Donahue JE, Stopa E, Hennessey JV, et al. Thyroid hormone levels in the prefrontal cortex of post-mortem brains of Alzheimer’s disease patients. Curr Aging Sci. 2008; 1:175–181. [PubMed: 20021390]
18. El Kholy M, Fahmi ME, Nassar AE, Selim S, Elsedfy HH. Prevalence of minor musculoskeletal anomalies in children with congenital hypothyroidism. Horm Res. 2007; 68:272–275. [PubMed: 17587855]
19. Sălăjea S, Gățăk-Ase-Kutsal Y, Celiker R, Erbas T, BaĂŸgĂﬂze O. Neuroelectrophysiological evaluation of untreated hyperthyroid patients. Thyroidology. 1994; 6:55–59. [PubMed: 7536451]
20. Cakir M, Samanci N, Balci N, Balci MK. Musculoskeletal manifestations in patients with thyroid disease. Clin Endocrinol (Oxf). 2003; 59:162–167. [PubMed: 12864792]
21. Øverlie I, Moen MH, Holte A, Finset A. Androgens and estrogens in relation to hot flushes during the menopausal transition. Maturitas. 2002; 41:69–77. [PubMed: 11809345]
22. Bowen RL, Smith MA, Harris PL, Kubat Z, Martins RN, et al. Elevated luteinizing hormone expression colocalizes with neurons vulnerable to Alzheimer’s disease pathology. J Neurosci Res. 2002; 70:514–518. [PubMed: 12391612]
23. Williams MB, Hernandez J, Thompson I. Luteinizing hormone-releasing hormone agonist effects on skeletal muscle: how hormonal therapy in prostate cancer affects muscular strength. J Urol. 2005; 173:1067–1071. [PubMed: 15758703]

24. Cumming DC, Wall SR, Galbraith MA, Belcastro AN. Reproductive hormone responses to resistance exercise. Med Sci Sports Exerc. 1987; 19:234–238. [PubMed: 3110538]

25. Hazeldine J, Arlt W, Lord JM. Dehydroepiandrosterone as a regulator of immune cell function. J Steroid Biochem Mol Biol. 2010; 120:127–136. [PubMed: 20060904]

26. Hogervorst E, Bandelow S, Moffat SD. Increasing testosterone levels and effects on cognitive functions in elderly men and women: a review. Curr Drug Targets CNS Neurol Disord. 2005; 4:531–540. [PubMed: 16266286]

27. Schiavone FE, Rietschel RL, Sgoutas D, Harris R. Elevated free testosterone levels in women with acne. Arch Dermatol. 1983; 119:799–802. [PubMed: 6225395]

28. Wichmann MW, Ayala A, Chaudry IH. Male sex steroids are responsible for depressing macrophage immune function after trauma-hemorrhage. Am J Physiol. 1997; 273:C1335–1340. [PubMed: 9357778]

29. Mason AS. The menopause: the events of the menopause. R Soc Health J. 1976; 96:70–71. [PubMed: 951489]

30. He C, Murabito JM. Genome-wide association studies of age at menarche and age at natural menopause. Mol Cell Endocrinol. 2012
Submit your next manuscript and get advantages of OMICS Group submissions

Unique features

- User friendly/feasible website-translation of your paper to 50 world’s leading languages
- Audio Version of published paper
- Digital articles to share and explore

Special features

- 300 Open Access Journals
- 25,000 editorial team
- 21 days rapid review process
- Quality and quick editorial, review and publication processing
- Indexing at PubMed (partial), Scopus, EBSCO, Index Copernicus and Google Scholar etc
- Sharing Option: Social Networking Enabled
- Authors, Reviewers and Editors rewarded with online Scientific Credits
- Better discount for your subsequent articles

Submit your manuscript at: http://www.editorialmanager.com/omicsgroup/
Figure 1.
Menopause Questionnaire assessing MHRT treatment and severity of symptoms.
Figure 2. Initial Assessment
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.
Figure 3. Follow-up Assessment
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.
Figure 4. Factor Analysis
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.
Figure 5. Factor Analysis
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.
Table 1
Significant Correlations of Hormones with MQ Symptom Domains.

| 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

J Genet Syndr Gene Ther. Author manuscript; available in PMC 2014 October 09.
### Table 2

Follow-up Assessment.

| 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       |