Preliminary Analysis of the Effect of Hormonal Shift on Immune Markers in Gulf War Illness Female Veterans

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BACKGROUND

Approximately one-third of Gulf War veterans returning from Operation Desert Storm (ODS) and Operation Iraqi Freedom (OIF) have since developed Gulf War Illness (GWI), a complex syndrome affecting multiple regulatory symptoms resulting in symptoms such as debilitating fatigue, musculoskeletal discomfort, skin rashes, and cognitive dysfunction. Although men with GWI have been extensively studied, we know less about women veterans with GWI due to the limited numbers of female veterans in pathogenesis studies. Moreover, as GWI female veterans are entering a phase of hormonal shift (Perimenopause to Menopause) it is not clear how hormone changes will interact with GWI induced immune disruptions. This preliminary analysis will focus on the effect of hormonal shift on immune markers in GWI female veterans.

METHODS

The inclusion criteria we follow in this study, derived from the case definition by Fukuda et al (1998), is as follows: A veteran deployed to the theater of operations between August 8, 1990 and July 31, 1991 with one or more symptoms present greater than six months from at least two of the following: fatigue; mood and cognitive complaints; and musculoskeletal complaints (joint pain, stiffness or muscle pain. Healthy Controls (HC) were matched to GWI controls by age (+/-5 years), sex, race/ethnicity and BMI (+/- 5).

Blood was collected across a 9-timepoint exercise challenge; however, this analysis will focus on baseline levels of key hormones and biomarkers.

Lymphocyte subset immunophenotyping (Navios Flow Cytometry) was used to count natural killer (NK) cells, B cells and T cells counts. **NK cell function** was determined using Chromium 51 release assay. **Hormone Levels** measured via Diasorin Liaison XL and Roche Assay platforms.

LEARNING OBJECTIVES

1. Determine changes in immune biomarkers in GWF compared to HCs.
2. Analyze the effect hormonal changes on key immune biomarkers in GWF
3. Discuss the impact of hormonal shifts on treatment options in GWF.

DEMOGRAPHICS

	GWF	HC
Sample Size (n)	27	27
Age (years)	54 (±7)	54 (±6)
Stated Menopause	NC*	16/27
Stated Estrogen Use	3/27	3/27
Hysterectomy	7/27	NC*

*NC=Not Captured

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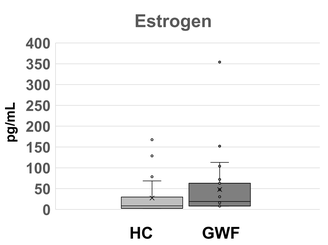
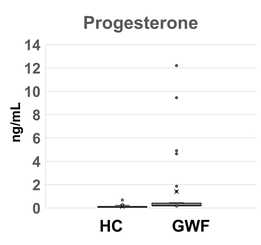
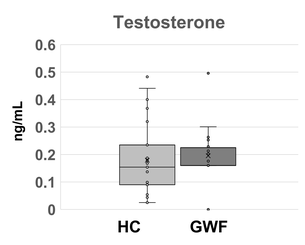
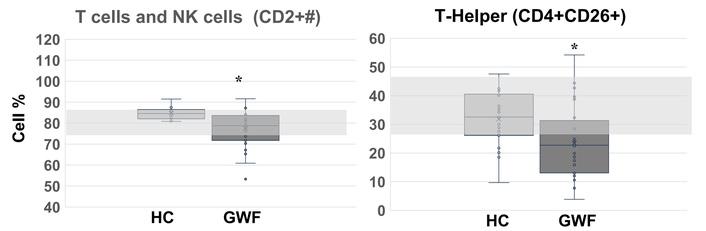
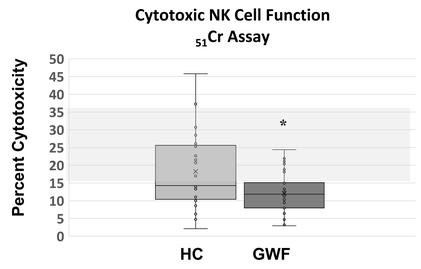
RESULTS

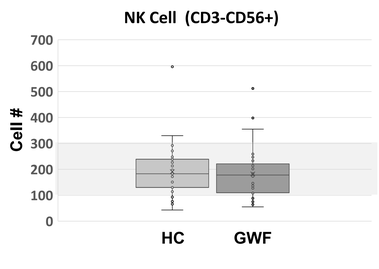


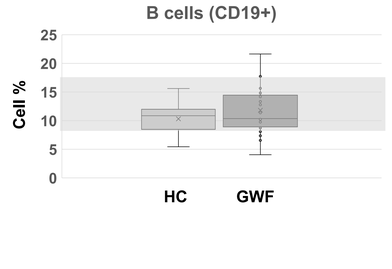


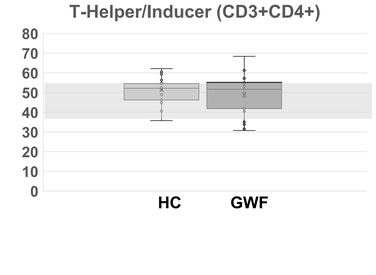




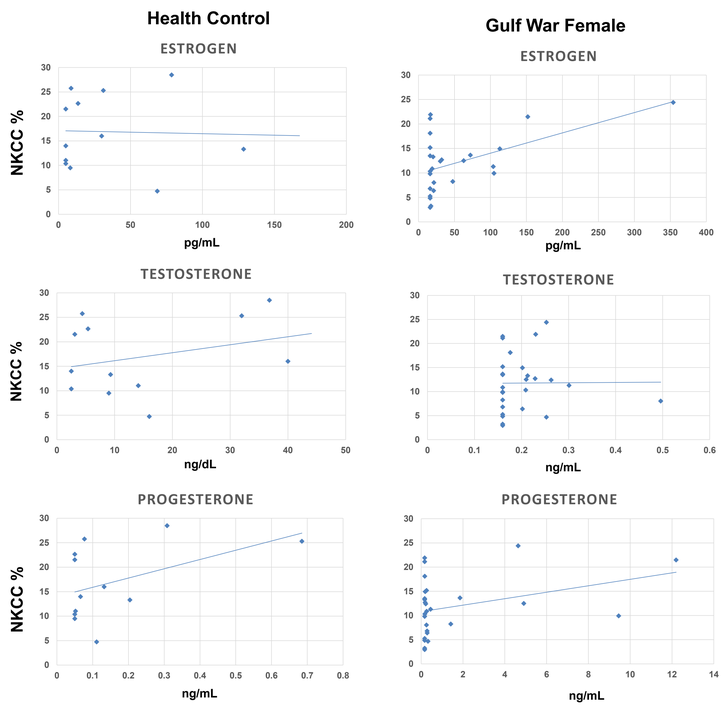




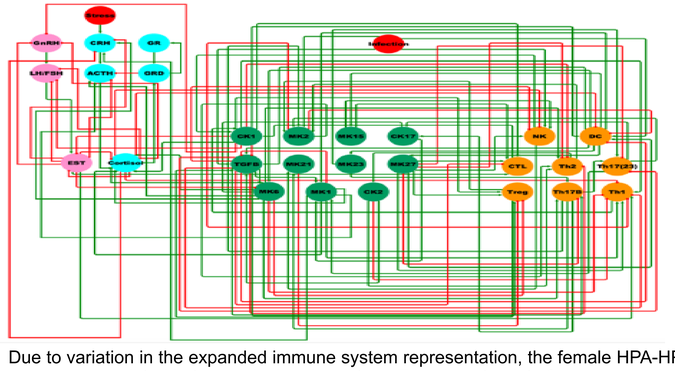


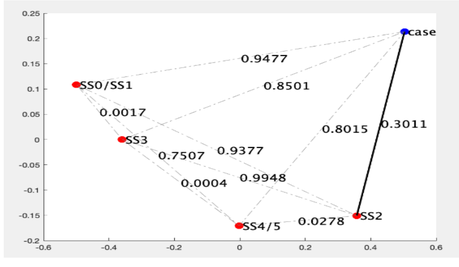


Correlation with Natural Killer Cell Function



COMPUTATIONAL ANALYSIS





Due to variation in the expanded immune system representation, the female HPA-HPG-immune system was afforded additional states beyond what was accommodated in the original male system. Experimental data for endocrine-immune markers measured in female GWI participants 47+ years of age showed alignment with predictions of naturally occurring alternate steady-state, suggesting that female GWI might be perpetuated at least, in part, by natural homeostatic regulation of the neuroendocrine-immune network. Unlike male GWI, female GWI aligned with a state characterized by hypercortisolism, low estrogen, and a shift towards a proinflammatory and Th2 immune response. Monte Carlo simulations coupled with a genetic algorithm machine learning optimization were applied to this female HPA-HPG-immune system starting from the predicted female GWI start state. As with the male model, no single intervention was available to reset the system, nor were there any dual intervention strategies identified. Rather, a three-treatment strategy was predicted: Estrogen/ progesterone supplementation followed by TNF suppression and glucocorticoid inhibition.

CONCLUSION

Data is now building on the lasting effect of GWI on female Veterans. 30+ years after the Gulf war women are still enduring fatigue, sleep problems, emotional and mental health problems; as well as immune dysfunctions. With the growing data accumulating from this initial study, modeling has produced treatment paradigms designed specifically for GWI women. The initial modeling suggests maintaining a hormone balance while rebooting the endocrine system.

SIGNIFICANCE TO VETERANS

Gulf War Illness is currently afflicting 250,000 gulf war-era veterans. Additionally, recent combat veterans are also returning home with similar ailments. The goal of this project is to develop safe and efficient treatments for women and men with Gulf War illness and other chronically ill veterans.