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Examining the Relationship between Stress and Insulin Resistance in Civilians and Veterans

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Abstract

Background: Stressful life events, particularly traumatic events, can produce a considerable if not significant stress, inducing insulin resistance and potentially type 2 diabetes mellitus (T2DM) secondary to hypercortisolism. However, the literature on individuals with Post-traumatic Stress Disorder (PTSD) or trauma exposure (TE) is inconclusive as to whether such conditions result in hyper- or hypocortisolism [1]. Recognizing the concern for complications resulting from hypercortisolism as a component of the stress response, further study for understanding individual variances in perception of stressors and coping was warranted. A study was conducted to examine and compare the influence of stressful life events on the development of T2DM in civilians and veterans.

Methods: The sample consisted of 40 civilians from SSM Health Centers and 39 veterans from VA Medical Centers in the greater St. Louis area subjects, diagnosed with T2DMin the previous six months, completed three surveys during an interview: The Recent Life Changes Questionnaire (RLCQ), the ENRICHD Social Support Instrument (ESSI), and a demographic survey that included BMI, genetic risk for diabetes (GRD), mental illness, and hemoglobin A1c (HbA1c) at time of diagnosis.

Results: The differences in BMI, GRD, and RLCQ scores between civilians and veterans were not significantly different. However, on average veterans in the sample had significant stress in the six months preceding their diagnoses of T2DM (308.9 LCU). There was a significant difference in HbA1c between civilians and veterans (t = 2.768, p = 0.007); a significant difference in the number of individuals within each group diagnosed with a mental illness (t = -2.227, p = 0.029); and a significant difference in the perception of social support (t = 1.997, p = 0.049). Analyses of the civilian (n = 40) and veteran (n = 39) subgroups separately showed that the relationship between RLCQ scores and mental illness was only significant for the veteran subgroup (t = -2.655, p = 0.012).

Discussion: The outcome of this study suggests that a significant portion of the veteran sample may have developed neurological changes as a result of events during the period of time in question prior to the diagnosis of T2DM, or preceding the study. With a lower perception of available social support, significant stress scores on average (> 300 LCU), and considerable number of veterans diagnosed with mental health disorders such as depression, PTSD, or a combination of the two, the ability to adapt to stressors may have been severely impacted.

Keywords

Stress, HPA axis, Veterans, Diabetes, Cortisol, Adaptation

Background

Coping mechanisms play an integral role in restoring homeostasis during times of physiological and psychological stress. The HPA axis acts as the conduit between an individual's conscious and or subconscious perceptions of stressors and the secretion of adrenal hormones - epinephrine, norepinephrine, aldosterone, and cortisol - that prepare the body for those stressors. Epinephrine, norepinephrine, and aldosterone preparing the body for the cardiovascular demands of the stressor by maintaining blood volume and oxygenation for cellular demands [2,3]. The resulting increase in cortisol levels promoting gluconeogenesis and glycogenolysis to aid in survival, particularly in mobilizing energy stores for the demands of the brain and heart [4,5].

Considering the Stress and Coping Framework proposed by Lazarus and Folkman [6], the physiological response to a stressor is comparable to primary appraisal. Whether an individual is simply startled or encounters a risk for harm, loss, threat, or a challenge, the stress response is activated and

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adrenal hormones are released. The duration of that activity depends on secondary appraisal of the stressor, which is influenced by the individual's perception of control over the stressor, degree of commitment to the threat posed by the stressor, and social support system. Perceiving a stressor can be controlled puts the individual at greater risk for guilt if the stressor is not resolved, and having a deep commitment to the impact of the stressor further complicates the matter as both factors present greater risk for hopelessness or despair [6].

The potential for new stressors to occur remains regardless of the occurrence of previous stressors. Unresolved stressors increase basal cortisol levels and new stressors increase the demand for coping. Mcewen [7] identified this phenomenon as allostatic load, the cost of adaptation. Frequent stress and repeated stressors of the same type with inefficient adaptation produce greater physiological demand for adrenal hormones such as cortisol and epinephrine.

A common sequela of prolonged hypercortisolism secondary to the stress response is insulin resistance. As stress can result from physical manifestations such as aerobic activity, illness, and physical trauma, as well as psychological manifestations such as depression, psychological trauma, and perception of life events, the potential for hypercortisolism and the resulting insulin resistance can be expected [8-12]. While the physiological response to stress is understood, the variances in individual responses and outcomes of stress are not as well understood.

Stressful life events, particularly traumatic events, can produce a considerable if not significant stress response as evidenced by the development of type 2 diabetes resulting from insulin resistance [9]. However, the literature on individuals with Post-traumatic Stress Disorder (PTSD) or trauma exposure (TE) are inconclusive as to whether such conditions result in hyper- or hypocortisolism, that in turn could influence insulin sensitivity [1].

Recognizing the concern for complications resulting from hypercortisolism as a component of the stress response, further study for understanding individual variances in perception of stressors and coping was warranted. A study was conducted to examine and compare the influence of stressful life events on the development of T2DM in civilians and veterans.

Methods

The research was conducted by using a quantitative and retrospective design with correlational and comparative aspects. The sample consisted of 40 non-veterans from SSM Health Centers and 39 veterans from VA Medical Centers in the greater St. Louis area. Inclusion criteria were: 18 years of age or older, a diagnosis of T2DM within the previous six months of the study, receiving outpatient diabetes care services from one of the selected medical centers, and willingness to participate in the research. Subjects recruited at SSM Health Centers were asked about veteran status as a part of screening for inclusion criteria.

Following informed consent, subjects completed three surveys during an interview taking at least 10 minutes. The demographic survey included data such as age, BMI, genetic risk for DM (GRD), HbA1c value at the time of T2DM diagnosis, co-existing mental health diagnoses such as depression or PTSD, ethnicity, gender, level of education, and marital status. Each subject's GRD was determined by asking if the subject had a parent, grandparent, or sibling with diabetes. The HbA1c value was used to measure the degree of insulin resistance that may have been influenced by stressful life events during the life of the red blood cells, 90-120 days.

Stress was measured in terms of stressful life events using the Recent Life Changes Questionnaire (RLCQ). The RLCQ consists of 73 life change events [13]. Subjects were asked to only consider the six months prior to their diagnosis of T2DM. If the subject experienced an event, the subject was given a predesignated score according to the survey. A score greater than or equal to 300 LCU in a period of 6 months is considered significant [13]. To ensure sufficient data for analysis, the authors recommended asking about 60 to 75 events in order to obtain 6-15 events that apply to the subject Rahe Reported that an unpublished test-retest run conducted four weeks apart showed acceptable reliability coefficients for the two subscales (α = 0.71 to 0.85). The reliability of the RLCQ in this study was 0.71.

Perception of social support was measured with the ENRICHD Social Support Instrument (ESSI). The ESSI consists of seven questions. The first question assesses the availability of someone to talk to and ranges from 1-5. The following six questions use dichotomous scoring for yes or no questions where subjects receive a score of one for no and two for yes. Total scores could range from 7-17. The ESSI demonstrated significant internal consistency reliability and inter-item associations (r = 0.94, α = 0.88, $p < 0.001$) and significant correlations in comparison to other social support instruments ($p < 0.05$) [14]. The reliability of the ESSI in this study was 0.74.

Demographic data were analyzed using descriptive statistics. Regression analyses were analyzed to determine the influence of age, BMI, GRD, stress (in terms of RLCQ scores), and presence of mental illness on HbA1c. Independent samples t-tests were analyzed to compare differences between civilians and veterans. Analyses were conducted with SPSS 25.

Limitation

Cortisol levels were not measured. The indirect measure of the expected influence of cortisol on HbA1c levels secondary to stress was deemed appropriate for this study.

Results

The average civilian subject was a 57-year-old, married, non-Hispanic, white male, who had at least a high school diploma, and a mother, father, or sibling with a known diagnosis of diabetes. The average subject's HbA1c was 8.9%, BMI was 33.2, stress score was 287.0 LCU, and had no history of mental illness. Removing the outliers for the subgroup, 21 subjects experienced six or more events with a mean RLCQ score of 432.1 LCU (SD = 146.2).

The average veteran subject was a 58-year-old, married, non-Hispanic, white male, who had a college degree, and a

Table 1: Demographic description of sample comparing civilian and veteran subjects.

	Overall (*N* = 79)	SSM (*n* = 40)		VA (*n* = 39)	
		Men (*n* = 23)	Women (*n* = 17)	Men (*n* = 31)	Women (*n* = 8)
Age in years $\bar{x}$ (SD)	57.63 (12.11)	52.70 (15.28)	62.29 (10.90)	59.87 (9.16)	53.25 (9.65)
BMI $\bar{x}$ (SD)	34.08 (6.63)	32.64 (7.91)	34.02 (6.12)	34.57 (5.92)	36.41 (6.49)
GRD *n*	61	16	13	24	8
Mental Illness *n*	29	3	7	12	7
Education *M*	Some College	High school Diploma	Some College	Some College	Some College/ College Degree
Married or Living with Partner *n*	42	13	6	21	2
Distress $\bar{x}$ (SD)	297.61 (201.98)	271.43 (192.68)	307.18 (198.64)	281.94 (213.79)	413.25 (181.61)
Social Support $\bar{x}$ (SD)	14.97 (2.30)	15.91 (1.38)	14.88 (2.15)	14.42 (2.73)	14.63 (2.45)
HbA1c $\bar{x}$ (SD)	8.31 (2.10)	9.26 (2.26)	8.48 (1.97)	7.80 (2.05)	7.18 (0.80)

Table 2: Correlations and T-tests for mental Illness, stress, and HbA1c.

	HbA1c & RLCQ (*r*; *p*)	HbA1c & MenIll (*r*; *p*)	RLCQ & MenIll (*r*; *p*)	T-test: MenIll & HbA1c	T-test: MenIll & RLCQ
Civilian Subgroup (*n* = 40)	r = -0.062, p = 0.703	r = -0.111, p = 0.496	r = 0.173, p = 0.286	t = 0.645, p = 0.529	t = -1.258, p = 0.222
Veteran Subgroup (*n* = 39)	r = -0.078, p = 0.638	r = -0.138, p = 0.402	r = 0.400, p = 0.012*	t = 0.848, p = 0.402	t = -2.655, p = 0.012*
Total (*N* = 79)	r = -0.083, p = 0.469	r = -0.188, p = 0.098	r = 0.302, p = 0.003**	t = 1.787, p = 0.078	t = -2.644, p = 0.011*

Note: RLCQ: Represents the mean amount of stress; MenIll: Mental Illness, * = $p < 0.05$, ** = $p < 0.01$

mother with a known diagnosis of diabetes. The average subject's HbA1c was 7.6%, BMI was 34.9, stress score was 308.9 LCU, and had no history of mental illness. Removing the outliers for the subgroup, 25 subjects experienced six or more events with a mean RLCQ score of 431.5 LCU (*SD* = 160.6). See (Table 1) for a more detailed comparison of the two groups.

The differences in BMI, GRD, and RLCQ scores between civilians and veterans were not significantly different. There was a significant difference in HbA1c between civilians and veterans (t = 2.768, p = 0.007); a significant difference in the number of individuals within each group diagnosed with a mental illness (t = -2.227, p = 0.029); and a significant difference in the perception of social support (t = 1.997, p = 0.049). There was not a significant difference in HbA1c levels nor ESSI scores between veterans with and without mental illness (t = 0.848, p = 0.402 and t = -0.873, p = 0.388).

For the sample (*N* = 79) there was a significant relationship between RLCQ scores and the presence of mental illness (r = 0.302, p = 0.003). Analyses of the civilian (*n* = 40) and veteran (*n* = 39) subgroups separately showed that the relationship between RLCQ scores and mental illness was only significant for the veteran subgroup (t = -2.655, p = 0.012). Further analysis of the influences of RLCQ scores and mental illness on HbA1c indicated no significant mediating effects (Table 2).

Discussion

Significant findings from the study pertained to the veteran subjects in the sample. On average veterans in the sample had significant stress in the six months preceding their diagnoses of T2DM (308.9 LCU) according to the RLCQ and had a lower perception of available social support according to the ESSI (t = 1.997, p = 0.049). Nearly twice as many veterans were diagnosed with a mental illness in comparison to civilians (t = -2.227, p = 0.029). The RLCQ scores were significantly higher for veterans with mental illness compared to veterans without mental illness (t = -2.655, p = 0.012). With the veteran sample having significantly lower HbA1c levels (t = 2.768, p = 0.007) in the presence of significant stress and mental illness, the relationship between stress and insulin resistance secondary to suspected hypercortisolism conflicts with literature on the relationship between stress and insulin resistance.

Considering the systematic reviews conducted by [1,2]. Regarding conditions such as melancholic depression and PTSD, the impact of such conditions on the HPA axis and cortisol secretion remains unclear [2] Found inconsistency in the results for elevated cortisol levels among studies comparing melancholic patients to non-melancholic patients or control groups. Speer, et al. [1] found consistency in the results suggesting that PTSD causes some form of dysregulation with HPA axis regulation, but controversy in how dysregulation develops and inconsistency in whether hypo- or hypercortisolism occurred as a result of PTSD remain. The respective study designs of the studies in the systematic reviews conducted by Juruena, et al. [2] and Speer, et al. [1] may have resulted in inconsistent findings as a result of individuals experiencing variances in glucocorticoid (GC) activity that influenced the outcomes of those respective studies and influenced the outcome of this study.

Adaptation is fundamental for the body to return to homeostasis with a reduction in the levels of free glucocorticoids (GCs) following a stress response. Factors such as GC sensitivity, bioavailability, receptors, and signaling pathways

influence multiple target tissues to prepare the body for increased physical demands. However, these factors can also lead to genomic changes resulting in reduced gene expression and interfere with transcriptional regulation [15]. In effect, hypercortisolism can reduce cellular productivity and receptor sensitivity. With GCs effecting multiple cellular functions that influence homeostasis, genomic changes could influence how an individual responds, or doesn't respond, to a stressor.

These genomic changes are comparable to Tull, et al. [16] description of emotional regulation occurring at the biological level. As expected with responding to a stressor, the HPA axis triggers the eventual release of GCs for general adaptation to a stressor, synonymous with the primary appraisal response discussed by Lazarus and Folkman [6]. Secondary appraisal requires reflection and analysis, utilizing the limbic center or pyramidal neuron hub of the brain that comprises the amygdala and hippocampus. With the process of resolution, negative feedback loops reduce HPA axis activity to the point of homeostasis [6,17]. A stressor that an individual cannot resolve can trigger a complex cascade of neurological restructuring where hypercortisolism eventually alters neural conduction, change GABAergic activity, and result in a damaging state of hyperpolarization that alters pyramidal neuron activity [18].

The outcome of this study suggests that a significant portion of the veteran sample may have developed neurological changes as a result of events during the period of time in question prior to the diagnosis of T2DM, or preceding the study. With a lower perception of available social support, significant stress scores on average (> 300 LCU), and considerable number of veterans diagnosed with mental health disorders such as depression, PTSD, or a combination of the two, the ability to adaptto stressors may have been severely impacted.

An individual's ability to appraise a stressor and determine choices for adaptation is a key step toward reducing HPA axis activity to the point of homeostasis. Inherent with the process of appraisal is reflection upon comparable past events, particularly in the case of trauma. While PTSD has specific criteria for diagnosis, the results of the systematic review conducted by Speer, et al. [1] suggest that the cases of hypocortisolism resulted from experience with a traumatic event when comparing PTSD groups with trauma-exposed (non-PTSD) groups, and not specifically as a result of the criteria associated with a diagnosis of PTSD.

Considering that an individual may not be able to adapt and recover from a traumatic experience, comparable stressors or events in the future that invoke recall of a traumatic experience may result in failure to adapt. Lazarus and Folkman [6] identified this state as hopelessness or despair; when an individual is unable to resolve or adapt to a stressor. This state is comparable to the "burnout syndrome" described by Bianchi, et al. [19]. Further study is needed to understand the implications of hopeless, despair, or the burnout syndrome in relation to HPA axis regulation and genomic changes associated with the hippocampus and amygdala.

Conclusion

How an individual responds to a stressor is comprised of physiological and psychological interactions that turn complex abstractions of experiences and thoughts into tangible cellular expressions toward effective coping or despair. Huxley [20] stated "Experience is not what happens to a [person]; it is what a [person] does with what happens to [him or her]" (p. 5). Whether he meant to sound optimistic or simply clever in describing experience, Huxley identified an essential aspect of coping. Individuals recover and move on from stressful experiences or remain burdened, unable to move forward and regain reasonable quality in their lives.

An individual that suffered a traumatic event may have a greater commitment to survival or avoidance of recurrence or event recall, especially in relation to the degree of threat or harm from the event [6]. In such cases, the addition of poorly- or unmanaged mental illness and limited social support in the presence of new stressful life events may result in (further) physiological decline with the development of chronic health conditions secondary to dysregulation of the HPA axis.

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