Associations between reduced telomere length, depressed mood, anhedonia, and irritability in prostate cancer patients: Further evidence for the presence of "male depression"?

Author

Sharpley, Christopher F, Christie, David RH, Bitsika, Vicki, Agnew, Linda L, Andronicos, Nicholas M, McMillan, Mary E

Published

2018

Journal Title

Psycho-Oncology

Version

Accepted Manuscript (AM)

DOI

10.1002/pon.4547

Associations between reduced telomere length, depressed mood, anhedonia, and irritability in Prostate Cancer patients: Further evidence for the presence of 'male depression'?

Christopher F Sharpley[1],
Brain-Behaviour Research Group,
University of New England, Armidale, Australia.
David R. H. Christie,
Genesiscare, Tugun, Queensland & Brain-Behaviour Research Group,
University of New England, Armidale, NSW, Australia.
Vicki Bitsika,
Centre for Autism Spectrum Disorders,
Bond University, Gold Coast, Australia.
Linda L Agnew,
Brain-Behaviour Research Group,
University of New England, Armidale, Australia.
Nicholas M Andronicos,
Brain-Behaviour Research Group,
University of New England, Armidale, Australia.
Mary E McMillan,
Brain-Behaviour Research Group,
University of New England, Armidale, Australia.

[1] Corresponding author: Brain-Behaviour Research Group, School of Science & Technology, University of New England, Queen Elizabeth Drive, Armidale, NSW, 2351, Australia. Ph: 61 2 6773 2596. Email: csharpl3@une.edu.au

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/pon.4547

Key points

1. Telomere length is associated with ill-health and poorer survival rates.
2. Male depression is characterised by irritability rather than sadness or anhedonia.
3. Measures of depressed mood, anhedonia, and irritability, plus telomere length, were taken in a sample of prostate cancer patients.
4. Irritability, but not depressed mood or anhedonia, was inversely correlated with telomere length.
5. The effects of male depression in prostate cancer patients may include genetic indicators of ill-health and mortality.

1,558 (excluding References)

The link between chronic stress and depression has been established for some time [1]. Major physical illness represents such a chronic stressor, and people who suffer from such illnesses have been shown to be at an increased risk of developing depression [2]. Perhaps one of the most feared of all illnesses is cancer [3]. Among Australian men, the most common form of cancer is prostate cancer (PCa) [4]. Meta-analytic data indicate that PCa patients suffer depression at a prevalence of 18.44% following treatment [5], several times higher than the 3-4% prevalence in men of similar ages from the general population [6]. Depression in PCa patients adds to their overall disease burden and may also impede their recovery from PCa [7]. Although most of the endpoints that have been measured in studies of depression in these men have been associated with medical and surgical costs, plus mortality [7], the links with the wider biological consequences of this elevated depression are also of value when formulating a comprehensive model of PCa depression.

One such biological consequence of depression is shortening of the telomeres in DNA, particularly in people who have undergone chronic stress [8]. Telomeres are regions of repetitive nucleotide sequence at the ends of linear chromosomes. Shortening of telomores has been shown to have widespread detrimental effects on health and lifespan, and to be associated with poorer survival rates [8]. Investigation of the possible effects of depression upon PCa patients' telomere lengths represents an additional potential indicator of the adverse sequalae of depression in these men.

Depression is commonly considered as a unitary construct, although there are nearly 1,500 ways in which the nine diagnostic criteria and associated features can fulfil the requirements for Major Depressive Disorder (MDD) [9], raising the issue of individualised MDD symptom profile analysis of depressed persons as a potential pathway to more effective treatment outcomes [10]. Of those nine diagnostic criteria for MDD, two hold key roles: depressed mood (sadness, crying, etc) and anhedonia (loss of interest and pleasure in most things). However, there is some evidence that the standard MDD diagnostic criteria may not

be as valid in men as some other symptoms, including irritability, fatigue and aggression [11]. Of those symptoms, irritability has been found to be the "best indicator of male depression" [12]. The relative association between telomere length and the two major traditional MDD symptoms compared to irritability (as an indicator of male depression) constitutes a potentially valuable target for investigation of the nature and effects of depression in men with PCa.

Methods

DNA was extracted from buccal mucosal cells (lining the inside of the cheeks) obtained from mouthwash samples provided by 103 PCa patients recruited for another study of cortisol and depression in PCa patients [13] with appropriate ethical approval. Patient responses to the first two items from the Patient Health Questionnaire-9 (PHQ9) [14] which measure anhedonia and depressed mood respectively, plus the irritability item from the Generalised Anxiety Disorder-7 (GAD7) [15] (see Table 1 for full wording of these three items) were also obtained at the time of the mouthwash sampling. PHQ9 and GAD7 item scores were on a four-point scale, where 1 = not at all, 2 = some days, 3 = more than half the days, 4 = nearly every day. Although MDD is most commonly measured by the whole nine criteria set out in the DSM-5 [6], there is evidence that use of a single-item to measure a well-defined construct is a valid procedure [16], [17], and each of the three items used in this study are parts of their respective scales and accepted as measuring the specific aspects of MDD and male depression that they address (i.e., anhedonia, depressed mood, irritability). Background data regarding cancer status and treatment were also collected. Measurement of mean telomere length was carried out using a standard polymerase chain reaction protocol [18].

Results

Data regarding patients' age and other background factors have been previously reported elsewhere [13]. Scores on the two PHQ9 items and the sole GAD7 item are shown in Table 1, plus data on patients' telomere lengths. There were no significant correlations between any of the background variables and PHQ9 or GAD7 items or telomere length. Table 2 presents the Spearman correlation coefficients (used because of the categorical nature of the PHQ9 and GAD7 item responses) between the key variables. As expected, there were significant correlations between the two PHQ9 items, and between these and the GAD7 item, but the only significant correlation between telomere length and any of these items was for the GAD7 item relating to patients' irritability. Although the absolute size of that correlation accounts for only a relatively small amount of the variance, the adjusted *p* value of .017 adopted via Bonferroni processes due to multiple significance testing (i.e., .05/3 = .0166) provides some support for the validity of this result.

Discussion

The finding that the depression-linked irritability experienced by these men was sufficiently severe as to be significantly correlated with reductions in telomere length, one of the major predictors of ill-health and shortened lifespan [8], is of considerable significance. That is, in addition to the effects of PCa itself, plus its treatment, upon these men's well-being, it appears that the development of (male) depression among some PCa patients may also be associated with a major genetic-based threat to their overall health. This finding also emphasises the seriousness of male depression in PCa patients and provides a basis for greater clinical focus upon male depression in these men. The comparison of the biological and psychological status and treatment outcomes of PCa patients suffering from traditional MDD versus those exhibiting male depression remains a significant clinical research target.

The finding that a well-documented outcome of chronic stress-linked depression (i.e., telomere length) was significantly correlated with the major indicator of male depression (i.e., irritability) but that the 'standard' major symptoms of MDD (i.e., depressed mood, anhedonia) were not, adds support to the hypothesis that male depression may be most accurately measured by reference to irritability rather than sadness or loss of interest and/or pleasure in usual activities [12]. The significant correlations between the GAD7 'irritability' item and the two major MDD symptoms measured by PHQ9 items 1 and 2 strengthens the argument that irritability in these men was an outcome of their overall depressive states rather than being due to extraneous causes. Future studies might include other major symptoms of male depression, although the point was made above that irritability is the "best indicator of male depression" [12].

Clinical implications

These findings hold several implications for the clinical management of PCa patients. First, they suggest that emphasis should be placed upon informal observations of PCa patients' irritability as well as on their major symptoms of MDD, perhaps even greater emphasis in the light of the previous findings mentioned above and these most recent results. Second, the inclusion of 'male depression' when formally screening PCa patients' mental health status is therefore supported by these findings as a way of more accurately identifying actual depression among these men and reducing the longevity and severity of their depression. Third, although there have been many attempts to assist PCa patients overcome their depression, those programmes were almost universally provided to men whose depression met the diagnostic criteria for MDD, which do not include a focus upon male depression. Application of those treatment models may automatically assume predominance of depressed mood or anhedonia rather than irritability, and may limit the efficacy of such treatments because of that misdiagnosis of the key symptoms of depression in these men.

None of the authors has any conflict of interest to declare

References

1. McEwan B. Glucocorticoids, depression, and mood disorders: structural remodeling in the brain. *Metabolism*. 2005; 54 (Supplement): 20-3.
2. Katon W, Lin E and Kroenke K. The association of depression and anxiety with medical symtpkm burden in patients with chronic medical illness. *General Hospital Psychiatry*. 2007; 29: 147-55.
3. Simard S, Thewes B, Humphris G, et al. Fear of cancer recurrence in adult cancer survivors: a systematic review of quantitative studies. *Journal of Cancer Survivorship*. 2013; 7: 300-22.
4. AIHW. Prostate cancer in Australia. *Cancer series*. Canberra: Australian Institute of Health & Welfare, 2013.
5. Watts S, Leydon G, Birch B, et al. Depression and anxiety in prostate cancer: a systematic review and meta-analysis of prevalence rates. *BMJ Open*. 2014; 4.
6. APA. *Diagnostic and Statistical Manual of Mental Disorders-5*. Washington, DC: American Psychiatric Association, 2013.
7. Jayadevappa R, Malkowicz S, Chhatre S, Johnson J and Gallo J. The burden of depression in prostate cancer. *Psycho-Oncology*. 2011; 21: 1338-45.
8. Wikgren M, Maripuu M, Karisson T, et al. Short telomeres in depression and the general population are associated with hypocortisolemic state. *Biological Psychiatry*. 2012; 71: 294-300.
9. Ostergaard S, Jensen S and Bech P. The heterogeneity of the depressive syndrome: When numbers get serious. *Acta Psychiatrica Scandinavia*. 2011; 124: 495-6.
10. Insel T. Transforming diagnosis. USA: National Institute of Mental Health, 2013, p. Post.
11. Rutz W, von Knorring L, Pihlgren H, Rihmer Z and Walinder J. Prevention of male suicides: lessons from Gotland study. *Lancet*. 1995; 345: 524.
12. Moller Leimkoller A, Heller J and Paulus N. Subjective well-being and 'male depression' in male adolescents. *Journal of Affective Disorders*. 2007; 98: 65-72.
13. Sharpley C, Christie D, Bitsika V, et al. The use of salivary cortisol as an index of chronic stress that correlates with depression in prostate cancer patients. *Psycho-Oncology*. in press.
14. Kroenke K, Spitzer R and Williams J. The PHQ-9: Validity of a brief depression severity measure. *Journal of General Internal Medicine*. 2001; 16: 606-13.
15. Spitzer R, Kroenke K, Williams J and Lowe B. A brief measure for assessing Generalised Anxiety Disorder. *Archives of Internal Medicine*. 2006; 166: 1092-7.
16. Gardner D, Cummings L, Dubham R and Pierce J. Single-item versus multiple-item measurement scales: An empirical comparison. *Educational and Psychological Measurement*. 1998; 58: 898-915.
17. Hoeppner B, Kelly J, Urbanoski K and Slaymaker V. Comparative utility of a single-item vs multiple item measure of self-efficacy in predicting relapse among young adults. *Journal of Substance Abuse and Treatment*. 2011; 41: 305-12.
18. O'Callaghan N and Fenech M. A quantitative PCR method for measuring absolute telomere length. *Biological Procedures Online*. 2011; 13.

Table 1

Scores on PHQ9 and GAD7 items, telomere length per telomere

Variable	Scores (*M*, SD, range)		
	Mean	SD	Range
PHQ9 item 1: Little interest or pleasure in doing usual activities	1.330	0. 492	1 to 3
PHQ9 item 2: Feeling down, depressed, or hopeless	1.270	0.524	1 to 4
GAD7 item 6: Becoming easily annoyed or irritable	1.53	0.639	1 to 4
Telomere length per telomere (kb)	3.559	1.950	0.585 to 8.978

Table 2

Spearman correlation coefficients between key variables

Variables	Telomere length (kb)	PHQ9 item 1	PHQ9 item 2	GAD7 item 6
Mean telomere length per telomere				
PHQ9 item 1: Little interest or pleasure in doing usual activities	-.037			
PHQ9 item 2: Feeling down, depressed, or hopeless	-.036	.295*		
GAD7 item 6: Becoming easily annoyed or irritable	-.238*	.276*	.367*	

*$p < .017$