Cortisol levels among older people with and without depression and dementia

Maria Lage Barca[1,2], Rannveig S. Eldholm[3,4], Karin Persson[1,2], Guro Hanevold Bjørkløf[1], Tom Borza[5], Elisabeth Telenius[1], Anne-Brita Knapskog[2], Anne Brækhus[1,2], Ingvild Saltvedt[3,4], Geir Selbæk[1] and Knut Engedal[1]

[1]Norwegian National Advisory Unit on Ageing and Health, Vestfold Hospital Trust, Tønsberg

[2]Department of Geriatric Medicine, Oslo University Hospital, Ullevål, Oslo

[3]Department of Neuromedicine and Movement Science, Norwegian University of Science and Technology (NTNU), Trondheim

[4]Department of Geriatrics, St. Olav Hospital, Trondheim

[5]Centre for Old Age Psychiatric Research, Innlandet Hospital Trust, Ottestad

Corresponding author:

Maria Lage Barca

Telephone: (+47) 9743-6610

E-mail: maria.barca@aldringoghelse.no

Post address: Norwegian Advisory Unit for Ageing and Health

Postbox 2136

3103 Tønsberg

Norway

Abstract

Cortisol dysregulation has been reported in dementia and depression. Cortisol levels and its associates were investigated among older people living at home and in nursing homes, in a cross-section study. A sample of 650 older people, from the community (home and nursing homes) and specialized care (memory clinics and old age psychiatry wards), mean age 76.8 (SD=10.3) (dementia n=319, depression, n=154, dementia plus depression n=53, reference group n=124), was included. Assessment included the Mini Mental State Examination (MMSE), Cornell scale for depression in dementia, activities of daily living scales and salivary cortisol. Number of drugs was registered. The results showed that the cortisol ratio was highest among patients with dementia and co-morbid depression in comparison to those with either depression or dementia and the reference group. Characteristics significantly associated with cortisol levels were higher MMSE score (in patients with dementia and co-morbid depression), male gender (in people with dementia) and number of medications (in the reference group). We conclude that the cortisol ratio was highest among patients with dementia and co-morbid depression in comparison to those with either depression or dementia and the reference group. The association of cortisol level with MMSE score among patients with dementia and depression could further indicate that increased stress is related to cognitive function.

Keywords: Health aging, depression, dementia, neuroendocrinology

Running title: Cortisol among older people and depression and dementia

Introduction

The relationship between depression and dementia is complex. Common patho-physiological pathways of the two disorders have been suggested, such as neuroinflammation and dysregulation of the hypothalamic-pituitary-adrenal axis (HPA). Cortisol is a hormone regulated by the HPA axis, mainly by corticotropin-releasing hormone (CRH). Additionally, the hippocampus has glucocorticoid receptors and contributes to regulation of cortisol levels. Higher cortisol levels have been reported as associated with depressive symptoms (Balardin et al., 2011). Indeed, dysregulation of cortisol has been found among Alzheimer's disease patients (Nasman et al., 1995). We therefore investigated if the co-existence of dementia and depression in the same older patient would boost cortisol levels. Our hypothesis was that cortisol levels are lowest among old persons without dementia and depression compared to those with either of the two conditions, and highest among patients with both conditions. Further, we investigated demographic and clinical characteristics associated with cortisol levels. To the best of our knowledge such a study has not yet been done.

Methods

Data from 650 subjects from four sources were included: 25 community-dwelling older persons without depression or cognitive impairment (Bjorklof et al., 2016), 169 patients referred for departments of old age psychiatry due to depression (Borza et al., 2015), 316 patients from three memory clinics (Barca et al., 2017), and 140 nursing home (NH) residents (Telenius et al., 2015). The data were pooled and divided into four diagnostic groups: a reference group of 124 older people without depression or cognitive impairment, 154 patients with depression (but without dementia), 319 patients with dementia (but without depression) and 53 patients with both conditions.

Assessment included the Mini-Mental Status Examination (MMSE) for global cognitive functioning and the Cornell Scale for Depression in Dementia (CSDD) for depressive

symptoms and classified as independent in function of daily living if they did not have any impairment of activities of daily living.

Patients from the memory clinics and the departments of old-age psychiatry were diagnosed with dementia and/or depression according to ICD-10 research criteria (WHO, 1993) by trained doctors. *The reference group* were classified as *not* having cognitive impairment with an MMSE score ≥ 27, and *not* having depression with a CSDD score <8. *The NH residents* were classified as *having* dementia by a MMSE score ≤ 23 and were considered to *have* depression if the CSDD score was ≥8. Number of drugs was registered.

Saliva cortisol levels were obtained using Salivette® three times in the same day (morning 7-9 a.m.; afternoon 12-2 p.m.; and evening 8-11 p.m.) to register the circadian rhythm. The participants (and health personnel caring for hospitalized patients and nursing home residents) were instructed to avoid drinking, eating, smoking, teeth brushing and training for at least one hour before collecting saliva with the salivette. The samples were returned to the research department and centrifuged before freezing at -20°. Cortisol levels were analysed using the competitive electrochemiluminescence (ECLIA) method. Cortisol ratio (evening /morning cortisol) was computed. Patients using prednisolone or other corticosteroids were excluded.

Differences between groups regarding patients' characteristics were analysed with Kruskal-Wallis and Mann-Whitney U-tests for continuous and $\chi 2$- test for categorical variables. We tested the hypothesis that cortisol levels were lowest for the reference group, higher for those with either depression or dementia and highest for those with both dementia and depression using Jonckheere–Terpstra test which is a test for ordered hypotheses. Multivariate linear regression analyses were performed. We first performed bivariate analyses between cortisol levels and the factors separately. Factors with significant associations ($p<0.20$) were entered in multivariate linear regressions, together with age and gender. All analyses were performed by IBM SPSS v22. Significance level was $p<0.05$.

All participants gave written consent to participate in the study, and the regional committees for ethics in medical research in south-eastern and northern Norway approved the study.

Results

The subjects of the four diagnostic groups were significantly different regarding demographic and clinical characteristics.

Cortisol ratio was highest in the patients with both dementia and depression compared to those with either depression or dementia and the reference group (Table 1). Results remained significant after exclusion of outliers. We further investigated which demographic and clinical characteristics were significantly associated levels cortisol levels. Adjusted models with significant associations ($p<0.05$) are shown in table 2.

Discussion

The aim of the present study was to investigate the hypothesis that cortisol levels would be lowest among old people without depression or cognitive impairment, higher among patients with either depression or dementia and highest among patients with both dementia and depression. We did not find such distribution of cortisol levels between the four diagnostic groups. It has been shown that higher cortisol levels are associated with depression (Balardin et al., 2011) and cognition, though the last has been controversial (Singh-Manoux et al., 2014, Souza-Talarico et al., 2009). We found higher cortisol ratio among patients with both dementia and depression as compared to those with either depression or dementia, and the reference group. Cortisol ratio is a rough measure of circadian rhythm. The fact that patients with both dementia and depression had higher cortisol ratio than the other groups indicates that they have a less steep slope of cortisol during the day than the other groups. This is contrary to what would be expected. It has been reported in the literature that patients

with dementia may present flattening of the circadian rhythm. However, one study has investigated the circadian rhythm of patients with advanced dementia and found that over half of these had preserved slope (Kovach et al., 2011). It might be that the difference in cortisol ratio between patient with dementia and co-morbid depression and the other group is due other characteristic than cognition.

By exploring which characteristics were significantly associated with the different cortisol levels in persons of the different diagnostic groups we found that among the elderly without depression or cognitive impairment, a higher number of drugs was significantly associated with higher levels of evening cortisol and the cortisol ratio. We did not have the number of diseases registered for all participants and therefore used number of drugs as an indirect measure of morbidity. The patients were healthy regarding depression and dementia, but might have other medical conditions that could explain higher cortisol levels. Indeed, altered cortisol levels have been found among frail elderly (Johar et al., 2014).

We also found that male gender was associated with higher cortisol levels among patients with dementia, both with depression and without depression and cortisol ratio among those with both conditions. One possible explanation for the increased levels of cortisol in men could be alterations in the adrenal androgens. Dehydroepiandrosterone (DHEA), its sulphate (DHAS) and its metabolite dehydroepiandrosterone sulfate (DHEAS) are the most abundant adrenal steroids in the circulation. Secretion of DHAS and dehydroepiandrosterone (DHA) decrease progressively from the third decade of life, a state called “adrenopause”. Lower levels of DHEAS in elderly men than women have been reported. It has been suggested that DHEA could possibly act as an antiglucocorticoid, and if that was the case, its decrease in men would lead to higher cortisol levels. One study has indeed found that male gender was a significant predictor of cortisol levels among patients with Alzheimer’s disease, even when adjusted for age (Nasman et al., 1995).

Among patients with dementia plus depression, higher MMSE score was significantly associated with higher evening cortisol levels. This is opposite to previous literature (Souza-

Talarico et al., 2009, Singh-Manoux et al., 2014). Patients with Alzheimer's dementia often have hippocampal atrophy. It has been shown that the hippocampus has glucocorticoid receptors that contribute to cortisol regulation. The atrophy of the hippocampus could therefore lead to dysfunctional regulation of cortisol and lower cortisol levels. And, glucocorticoids are toxic to hippocampal neurons, leading to increased atrophy, in a vicious cycle. The relationship between depression, cognitive impairment and cortisol has only been published in one study. That study found that high cortisol levels led to incident cognitive impairment in patients with depression or anxiety, but not in those without (Potvin et al., 2013). It is known that depression in dementia is related to awareness of the disease (Migliorelli et al., 1995) and it could be that patients with higher MMSE were more aware of their disease and therefore became more stressed, leading to higher evening cortisol.

This study has some limitations. We recruited patients from different sources and studies with different inclusion criteria, we did not have cortisol levels for all 650 persons, not all patients were evaluated according to ICD-10 criteria for dementia and depression, and we lacked a matched reference group.

The strengths of the study are the high number of patients included and the use of well-established and validated instruments to classify participants according to the presence of dementia and depression.

Conclusion

The cortisol ratio was higher among patients with depression and dementia than those with either depression or dementia and the reference group. The association of cortisol ratio with gender among patients with dementia plus depression could further indicate that there are other pathways than cognition involved in the circadian rhythm.

Conflicts of interest: None.

Description of authors' roles: Maria Barca designed the study, collected part of the data, performed the statistical analyses and wrote the paper. Rannveig S. Eldholm collected part of the data and assisted in writing the paper, Karin Persson collected part of the data and assisted in writing the paper, Guro Hanevold Bjørkløf collected part of the data and assisted in writing the paper, Tom Borza collected part of the data, assisted in the design of the study and in writing the paper, Elisabeth Telenius collected part of the data, assisted in designing the study and in writing the paper, Anne-Brita Knapskog collected part of the data and assisted in writing the paper, Anne Brækhus collected part of the data and assisted in writing the paper, Ingvild Saltvedt assisted in writing the paper, Geir Selbæk assisted in writing the paper and Knut Engedal supervised the designing of the study and analyses of the data and assisted in writing the paper.

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References

BALARDIN, J. B., VEDANA, G., LUZ, C. & BROMBERG, E. 2011. Subjective mild depressive symptoms are associated with abnormal diurnal cycle of salivary cortisol in older adults. *J Geriatr Psychiatry Neurol,* 24**,** 19-22.

BARCA, M. L., PERSSON, K., ELDHOLM, R., BENTH, J. S., KERSTEN, H., KNAPSKOG, A. B., SALTVEDT, I., SELBAEK, G. & ENGEDAL, K. 2017. Trajectories of depressive symptoms and their relationship to the progression of dementia. *J Affect Disord,* 222**,** 146-152.

BJORKLOF, G. H., ENGEDAL, K., SELBAEK, G., MAIA, D. B., COUTINHO, E. S. & HELVIK, A. S. 2016. Locus of control and coping strategies in older persons with and without depression. *Aging Ment Health,* 20**,** 831-9.

BORZA, T., ENGEDAL, K., BERGH, S., BENTH, J. S. & SELBAEK, G. 2015. The course of depression in late life as measured by the Montgomery and Asberg Depression Rating Scale in an observational study of hospitalized patients. *BMC Psychiatry,* 15**,** 191.

JOHAR, H., EMENY, R. T., BIDLINGMAIER, M., REINCKE, M., THORAND, B., PETERS, A., HEIER, M. & LADWIG, K. H. 2014. Blunted diurnal cortisol pattern is associated with frailty: a cross-sectional study of 745 participants aged 65 to 90 years. *J Clin Endocrinol Metab,* 99**,** E464-8.

KOVACH, C. R., WOODS, D. L., LOGAN, B. R. & RAFF, H. 2011. Diurnal variation of cortisol in people with dementia: relationship to cognition and illness burden. *Am J Alzheimers Dis Other Demen,* 26**,** 145-50.

MIGLIORELLI, R., TESON, A., SABE, L., PETRACCHI, M., LEIGUARDA, R. & STARKSTEIN, S. E. 1995. Prevalence and correlates of dysthymia and major depression among patients with Alzheimer's disease. *Am J Psychiatry,* 152**,** 37-44.

NASMAN, B., OLSSON, T., VIITANEN, M. & CARLSTROM, K. 1995. A subtle disturbance in the feedback regulation of the hypothalamic-pituitary-adrenal axis in the early phase of Alzheimer's disease. *Psychoneuroendocrinology,* 20**,** 211-20.

POTVIN, O., FORGET, H., PREVILLE, M., BERBICHE, D., CHAGNON, Y. C. & HUDON, C. 2013. Relationship between cortisol level and prevalent/incident cognitive impairment and its moderating factors in older adults. *Int Psychogeriatr,* 25**,** 252-62.

SINGH-MANOUX, A., DUGRAVOT, A., ELBAZ, A., SHIPLEY, M., KIVIMAKI, M. & KUMARI, M. 2014. No evidence of a longitudinal association between diurnal cortisol patterns and cognition. *Neurobiol Aging,* 35**,** 2239-45.

SOUZA-TALARICO, J. N., CHAVES, E. C., NITRINI, R. & CARAMELLI, P. 2009. Chronic stress is associated with high cortisol levels and emotional coping mechanisms in amnestic mild cognitive impairment. *Dement Geriatr Cogn Disord,* 28**,** 465-70.

TELENIUS, E. W., ENGEDAL, K. & BERGLAND, A. 2015. Effect of a high-intensity exercise program on physical function and mental health in nursing home residents with dementia: an assessor blinded randomized controlled trial. *PLoS One,* 10**,** e0126102.

WHO, World Health Organization (ed.) 1993. *The ICD-10 Classification of Mental and Behavioural Disorders: diagnostic criteria for research*.

Table 1. Patient characteristics						
	All N=650	**Reference N=124**	**Depression N=154**	**Dementia N=319**	**Dementia and depression N=53**	**p-value**
Age, n=649, mean (SD)	76.8 (10.3)	68.8 (11.5)	76.5 (6.9)	79.1 (9.2)	83.0 (9.4)	<0.001[1]
Women, n=650, n (%)	399 (61.4)	61 (49.2)	113 (73.4)	184 (57.7)	41 (77.7)	<0.001[2]
MMSE sum, n=636, mean (SD)	21.9 (6.8)	28.5 (2.0)	26.6 (3.0)	18.2 (6.3)	16.7 (5.3)	<0.001[1]
Cornell Sum, n=601, mean (SD)	6.6 (6.9)	2.4 (2.9)	15.2 (7.2)	3.9 (3.7)	12.2 (4.5)	<0.001[1]
Independent in ADL, n=629, n (%)	86 (13.7)	47 (42.3)	23 (15)	15 (4.8)	1 (1.9)	<0.001[2]
Cortisol morning (nmol/L), n=467, median (range)	15.0 (0-306)	14.7 (4.1-152.8)	17.5 (3.9-56.3)	14.1 (0.0-306.4)	14.4 (3.7-96.9)	0.237[3]
Cortisol afternoon, (nmol/L) n=492, median (range)	7.2 (0-409)	6.9 (2.9-408.8)	8.6 (2.5-30.4)	6.7 (0-174)	7.8 (1.4-36.7)	0.625[3]
Cortisol evening, (nmol/L) n=480, median (range)	5.1 (0-243)	5.3 (1-42.8)	5.3 (0.5-19.1)	4.9 (0-242.9)	5.7 (1.9-36.5)	0.236[3]
Cortisol ratio (evening/morning), n=496, median (range)	0.34 (0-17.8)	0.45 (0.05-2.3)	0.36 (0.02-1.9)	0.36 (0-17.8)	0.49 (0.12-1.5)	0.014[3]
Number of drugs, n=634, mean (SD)	5.0 (3.2)	3.3 (2.6)	6.0 (2.9)	5.0 (3.3)	6.5 (3.6)	<0.001[1]

[1]Kruskal-Wallis Test

[2]$\chi 2$- test

[3]Jonckheere–Terpstra test

Table 2. Multiple linear regression analysis of associations between cortisol and patient characteristics.								
	Morning cortisol		**Afternoon cortisol**		**Evening cortisol**		**Cortisol ratio**	
	β	**P value**	**β**	**P value**	**β**	**P value**	**β**	**P value**
Reference group (N=124)								
(Constant)						0.180		0.164
Age					-0.025	0.805	-0.014	0.896
Gender					0.092	0.357	0.063	0.540
Number of medications					**0.286**	**0.006**	**0.271**	**0.011**
Independent					NS	NS	-0.158	0.128
R^2 (%)					9.0		10.4	
Dementia (n=319)								
(Constant)				0.175				
Age			-0.036	0.582				
Gender (female=0, male=1)			**0.141**	**0.033**				
R^2 (%)			2.3					
Dementia plus depression (n=53)								
(Constant)						0.777		0.671
Age					0.047	0.773	0.103	0.534
Gender (female=0, male=1)					**0.325**	**0.037**	**0.398**	**0.021**
MMSE					**0.336**	**0.037**	NS	NS
R^2 (%)					19.3		14.8	

Only models with significant associations are shown

NS: non-significant