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Short Communication

The impact of glucocorticoid medication use on hair cortisol and cortisone in older adults: Data from the Irish Longitudinal Study on Ageing

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ABSTRACT

Research focusing on the hair concentration of cortisol and cortisone has significantly developed over the last two decades and has huge potential to provide relevant insights into stress-related diseases. However it is not clearly understood exactly how glucocorticoid (GC) medications, which are commonly prescribed drugs particularly among older adults, may affect hair cortisol and cortisone levels. The aim of this study was to examine associations of the use of GC medications with hair cortisol and cortisone concentrations in a sample of older adults. Hair samples and data were collected from participants at Wave 3 of The Irish Longitudinal Study of Ageing (TILDA). Results showed that before and after controlling for socio-demographic, health and hair characteristics, the use of systemic GCs was associated with decreased hair cortisone (B= -0.34 95 % CI -0.53, -0.16, $p < 0.001$). However, the use of local GCs was associated with increased hair cortisol (B = 0.39 95 % CI 0.18, 0.61). Further analysis suggests that the latter finding may be the result of use of topical steroid creams/ointments. These data add to the scant literature on the impact of steroid medication use on hair cortisol and cortisone in non-clinical populations, providing further evidence that future hair GC studies need to consider steroid medication use.

1. Introduction

The glucocorticoid (GC) hormone cortisol is produced by activation of the hypothalamic-pituitary-adrenal (HPA) axis in response to the perception of a stressor, and is responsible for regulating metabolic, immune, inflammatory and stress processes throughout the body (Walker and Seckl, 2001). Although production of cortisol is necessary to trigger normal responses to threat and re-establish homeostasis, changes in cortisol signalling associated with prolonged stress increases the risk of chronic disease (Chrousos, 2009).

In contrast with standard measures for assessing the physiological response to acute stress, such as those obtained from blood, saliva and urine samples, the measurement of GCs in hair allows retrospective estimation of longer-term stress reactivity (Gow et al., 2010; Wosu et al., 2013). While relatively little is known about the physiological significance of cortisone, it seems that under certain circumstances cortisone could more closely approximate unbound, biologically active cortisol than total cortisol levels (Perogamvros et al., 2010). Thus it has been argued that a simultaneous measurement of cortisone and cortisol levels provides a thorough assessment of both active and inactive GCs (Zhang et al., 2018). Previous studies have explored associations between elevated hair GCs and cognitive outcomes, mental health, cardiovascular diseases and other health conditions (Feeney et al., 2020; Wosu et al., 2013). Furthermore, the concentrations of hair GCs are known to be influenced by other factors including hair type and treatment (Wosu et al., 2013).

Evidence shows that steroid medications inhibit the normal function of the HPA axis and alter the body's concentration of endogenous cortisone and cortisol (Broersen et al., 2015; Cirimele et al., 2000). Nonetheless, these drugs are widely used in human therapy for their anti-inflammatory, anti-allergic and immunosuppressive properties. Use of GC medications is particularly widespread among older adults, for whom they are often prescribed as treatment for a heterogeneous group of health conditions, needing diverse dosages, durations of use and routes of administration (Broersen et al., 2015; Van Staa et al., 2000).

The first studies focusing on the measurement of steroid compounds in hair were investigations of doping in athletics, and evidence from these confirmed that exogenous corticosteroids are incorporated into human hair (Cirimele et al., 2000). Contrasting findings have recently emerged regarding the *direction* of the association between exogenous and endogenous GCs, however evidence, particularly from cohort

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studies, is limited and contradictory (Abell et al., 2016; Wester et al., 2017).

Due to the rapidly increasing amount of research focused on hair cortisol (and more recently cortisone also), and the widespread use of GC medications among older adults, it is important to understand the influence of steroid medication use on hair GC concentrations. To the best of our knowledge only one other study has investigated this in a similarly large population-based sample of older adults (Abell et al., 2016), and the authors did not measure cortisone in addition to cortisol. We aimed to investigate 1) the relationship between any GC medication use and hair concentrations of cortisol and cortisone, and, 2) whether and how results vary according to the route of administration.

2. Methods

Data analysed in this study was collected on Wave 3 of The Irish Longitudinal Study on Ageing (TILDA). More information about the TILDA cohort design has been published elsewhere (Donoghue et al., 2018). Briefly, TILDA is a nationally representative prospective cohort study, examining socio-demographic, economic and health characteristics of adults aged over 50 years old in the Republic of Ireland. Data collection at Wave 3 included a computer-assisted personal interview (CAPI), a self-completion questionnaire and a comprehensive health assessment. Ethical approval was obtained from the institutional review board and all respondents provided signed informed consent before participating in the study.

2.1. Hair sample collection and analysis

During the health assessment, hair samples were collected from the participants' posterior vertex of the head and as close as possible to the scalp. Samples were analysed by liquid chromatography-tandem mass spectrometry (LC–MS/MS) by the Dresden Lab Service GmbH at the Technical University of Dresden in Germany (Gao et al., 2013). Only hair samples weighing over 7.5 mg were considered for analysis. Hair cortisol and cortisone concentration was reported in pg/mg.

2.2. GC medication use

Information about any use of steroid and hormone medications within the last four months was collected at the time of hair sampling via questionnaire. Answer options were: None / Hormone replacement therapy / Cortisone cream / Steroid inhaler / Prednisone / Contraceptive hormones / Other (please specify). Answers were firstly coded into 2 groups: users of any type of GCs medications versus non-users; then further into 4 groups taking into account the route of administration. This allowed us to identify: users of local GCs (including ointments and topical creams, inhaled medications, nasal/eye/ear drops and joint injections), systemic GCs users (oral/parenteral medications), and concomitant users (those using both local and systemic GCs). Participants lacking information on the GC route of administration were considered in the first categorisation but excluded from the second.

2.3. Covariates

Consideration was given to socio-demographic and health characteristics that were related to both endogenous glucocorticoids and likelihood of steroid containing medication use. Information on sex, age, education and smoking was collected through CAPI. Participants were also asked whether they had ever received a doctor's diagnosis of any of a list of cardiovascular conditions. BMI (kg/m^2) was assessed and defined as: normal weight (BMI > 18.5–24.9), overweight (BMI 25–29.9) and obese (BMI $\geq$ 30). Frequency of shampooing, use of hair chemical treatments and season of sample collection were also recorded.

2.4. Statistical analysis

Exclusion criteria included hormone replacement therapy during the previous 4 months (N = 74), Addison's disease (N = 2), pituitary tumour (N = 1), and being underweight (N = 22). Analysis was conducted on participants with detectable hair levels of cortisol and/or cortisone, who completed the questionnaire related to hair characteristics and steroid medication use, and had available data on covariates. The number of participants included varied slightly between models due to a small difference in the number of hair samples with detectable cortisol versus cortisone. Variation in the sample size also occurred because in the second analysis, we excluded 4 individuals for whom it was possible to identify GC use but not route of administration, and 17 individuals with concomitant GC use by contrasting routes of administration.

Hair cortisone and cortisol concentrations were positively skewed and were log transformed prior to analysis. Linear regression was used to determine associations between GC medication use and hair cortisol and cortisone. We first ran an unadjusted model, followed by a second model controlling for age, gender and hair characteristics, and finally a third model adding adjustment for BMI, diabetes, CVD count and smoking status. We excluded cortisone and cortisol outliers 3SD from the mean for each group; however for completeness, desriptive statistics and results of regression models with outliers retained are also reported in Supplementary Data (Table A and B).

All statistical analyses were performed using SPSS 25.

3. Results

Table 1 shows the socio-demographic and health characteristics of the participants after exclusions (N = 2082). Mean age of participants was 66 years, with a majority of female participants (76 %). Eleven percent of the participants were taking a GC medication (see Table 1 for full description).

The geometric mean for hair cortisol among non-users was 6.8 pg/mg (95 % CI 6.4, 7.2), and among GC users it was 9.7 pg/mg (95 % CI 7.7, 12.2). The hair cortisone geometric mean was 9.0 pg/mg (95 % CI 8.7, 9.3), among non-users and 8.1 pg/mg (95 % CI 7.2, 9.0) among users.

Table 2 shows the results of the regression analyses. After both minimal and full adjustment for potential confounders, hair cortisol was significantly increased in GC users. When this was further explored by route of administration, cortisol was found to be significantly higher in local GC users compared with non-users (B = 0.39, 95 % CI 0.18, 0.60, $p < 0.001$, fully adjusted model).

On the contrary, we found significantly lower hair cortisone in all GC users versus non-users. Further analysis revealed that individuals taking GC medications by systemic route had lower cortisone (B = -0.34, 95 % CI -0.53, -0.16, $p < 0.001$). There was no significant difference in cortisol concentrations between local GC users and non-users.

3.1. Sensitivity analysis

We further analysed the impact of use of topical steroid creams on cortisol, to determine whether this explained the positive association with local GC use. Individuals who reported using cortisone- or other steroid-containing cream (N = 58) had significantly elevated hair cortisol compared to non-GC users (geometric mean = 18.28, 95 %CI 10.02, 33.32). Excluding these individuals from the regression analyses with cortisol as the explanatory variable rendered the association between local GC use and cortisol non-significant. Moreover, the size of the beta coefficient associated with local GC use was markedly decreased after exclusion of topical steroid users, from 0.39 to 0.06 (Table 3).

Table 1
Socio-demographic and health characteristics of the sample (N = 2082).

	Mean (SD)/N (%)	Cortisol (log, pg/mg)		Cortisone (log, pg/mg)	
		Mean (SD)	p	Mean (SD)	p
Age	66 (9)				
Sex					
Female	1576 (76)	1.87 (1.37)		2.06 (0.72)	
Male	506 (24)	2.21 (1.34)	< 0.001	2.58 (0.56)	< 0.001
Hair characteristics					
Shampooing frequency					
Less than once a week	129 (6)	2.26 (1.48)		2.36 (0.54)	
1 − 3 times a week	652 (31)	2.04 (1.40)		2.22 (0.68)	
3 − 4 times a week	957 (46)	1.89 (1.35)		2.15 (0.76)	
4 − 6 times a week	150 (7)	1.84 (1.36)		2.05 (0.79)	
Daily	194 (9)	1.88 (1.25)	0.011	2.22 (0.72)	0.002
Hair chemical treatment					
Yes	1171 (56)	1.80 (1.39)		1.94 (0.74)	
No	911 (44)	2.15 (1.32)	< 0.001	2.50 (0.57)	< 0.001
Season of collection					
Spring	441 (21)	1.88 (1.31)		2.16 (0.68)	
Summer	588 (28)	1.86 (1.41)		2.15 (0.73)	
Autumn	700 (34)	2.04 (1.34)		2.25 (0.74)	
Winter	353 (17)	2.02 (1.43)	0.067	2.13 (0.71)	.044
Health characteristics					
BMI					
Normal-weight	533 (26)	1.86 (1.39)		2.08 (0.73)	
Overweight	884 (42)	1.95 (1.36)		2.17 (0.70)	
Obese	665 (32)	2.03 (1.36)	.125	2.29 (0.73)	< 0.001
Diabetes					
No	1916 (92)	1.92 (1.35)		2.16 (0.72)	
Yes	166 (8)	2.31 (1.50)	< 0.001	2.42 (0.69)	< 0.001
CVD count					
None	782 (38)	1.81 (1.31)		2.11 (0.74)	
1	677 (32)	1.96 (1.40)		2.18 (0.71)	
> 2	623 (30)	2.13 (1.39)	< 0.001	2.28 (0.70)	< 0.001
Smoking					
Never smoker	1000 (48)	1.84 (1.32)		2.13 (0.72)	
Ex-smoker	850 (41)	2.07 (1.41)		2.21 (0.74)	
Current smoker	232 (11)	2.01 (1.40)	0.002	2.33 (0.70)	< 0.001
Glucocorticoid (GC) use					
None	1846 (89)	1.91 (1.30)		2.19 (0.71)	
Any GC medication	236 (11)	2.27 (1.79)	< 0.001	2.09 (0.85)	.035
Local administration	165 (8)	2.32 (1.75)		2.13 (0.77)	
Systemic administration	50 (2)	1.90 (1.75)	0.001[b]	1.87 (1.02)	0.005[b]
Single route not established[a]	21(1)	2.68 (1.99)		2.20 (0.95)	

[a] Route of administration could not be established or use of concomitant medications with more than one route of administration.
[b] Comparison of local GC users, systemic GC users and non-users.

Table 2
Associations between use of glucocorticoid medications and hair concentrations of cortisone and cortisol.

	Model 1				Model 2				Model 3			
	Coefficient	95 % CI		p-value	Coefficient	95 % CI		p-value	Coefficient	95 % CI		p-value
Cortisol (N = 2020)		Lower	Upper			Lower	Upper			Lower	Upper	
No GC medication	*Reference*				*Reference*				*Reference*			
Any GC medication	**0.36**	0.17	0.54	< 0.001	**0.35**	0.16	0.53	< 0.001	**0.32**	0.13	0.51	0.001
Cortisol (N = 2001)												
No GC medication	*Reference*				*Reference*				*Reference*			
Systemic GC medication	−0.01	−0.40	0.38	0.963	−0.04	−0.43	0.34	0.834	−0.06	−0.45	0.32	0.755
Local GC medication	**0.41**	0.19	0.63	< 0.001	**0.41**	0.20	0.63	< 0.001	**0.39**	0.18	0.61	< 0.001
Cortisone (N = 2042)												
No GC medication	*Reference*				*Reference*				*Reference*			
Any GC medication	**−0.11**	−0.21	−0.01	0.035	**−0.10**	−0.19	−0.01	0.036	**−0.11**	−0.20	−0.02	0.019
Cortisone (N = 2020)												
No GC medication	*Reference*				*Reference*				*Reference*			
Systemic GC medication	**−0.33**	−0.54	−0.12	0.002	**−0.33**	−0.52	−0.14	0.001	**−0.34**	−0.53	−0.16	< 0.001
Local GC medication	−0.06	−0.17	0.06	0.329	−0.05	−0.15	0.06	0.373	−0.06	−0.16	0.05	0.300

Model 1: Unadjusted | Model 2: Adjusted for sex, age, hair characteristics | Model 3: Adjusted for sex, age, hair characteristics, BMI, diabetes, smoking, CVD count; GC: glucocorticoid. Note: Values of cortisol and cortisone are log transformed.

Table 3
Associations between use of glucocorticoid medications and hair concentrations of cortisone and cortisol excluding users of steroid-containing creams.

	Model 1				Model 3			
	Coefficient	95 % CI		p-value	Coefficient	95 % CI		p-value
Cortisol (N = 1946)								
No GC medication	*Reference*				*Reference*			
Systemic GC medication	−0.01	−0.39	0.37	0.962	−0.05	−0.43	0.32	0.772
Local GC medication	**0.09**	−0.17	0.34	0.507	**0.06**	−0.19	0.32	0.607
Cortisone (N = 1965)								
No GC medication	*Reference*				*Reference*			
Systemic GC medication	**−0.33**	−0.54	−0.12	0.002	**−0.35**	−0.54	−0.16	0.000
Local GC medication	−0.09	−0.24	0.04	0.183	−0.08	−0.20	0.05	0.244

Model 1: Unadjusted | Model 3: Adjusted for sex, age, hair characteristics, BMI, diabetes, smoking, CVD count; GC: glucocorticoid. Note: Values of cortisol and cortisone are log transformed.

4. Discussion

In a large population-based sample of older adults we found that systemic GC use was associated with lower hair cortisone when compared with individuals taking no GC medications, indicating HPA axis suppression. Conversely, elevated cortisol (but not cortisone) was observed in individuals taking GC medications by a local route of administration. However, this difference disappeared after exclusion of anyone using topical steroid creams or ointments, suggesting that the high cortisol values are due to topical steroid use.

To the best of our knowledge, only two other cohort studies of older adults have investigated the impact GC medication use on hair cortisol/cortisone. Our results partly accord with findings from both. Abell et al. (2016) found higher hair cortisol levels among individuals from the Whitehall II study who were taking systemic GC medications (they did not measure hair cortisone). We were not able to replicate this finding; however, the authors reported that when outliers were retained, systemic CG therapy was associated with lower cortisol whereas topical steroid use was associated with higher cortisol. We also find that topical steroids are associated with higher cortisol (even after outlier removal). Though we didn't observe any effect of systemic GC use on hair cortisol we did find decreased cortisone in this group. This is consistent with the findings of Wester et al. (2017), who reported lower hair cortisone among systemic GC users, however in contrast to our results, they also found lower cortisone among local GC users. The reasons for some discrepant findings between the three studies are not clear but may be due to sample differences. For example, Wester et al. sampled younger individuals (mean age 42) than the other two studies, and the small sample size meant the numbers of individuals taking GC medications were extremely low, rendering the results more susceptible to influence from particular individuals. In the Whitehall II study, as determining the impact of steroid medication use on hair cortisol was not the main aim, detail is lacking as to how local and systemic medications were defined which may have led to differences in group assignment between studies.

Adrenal suppression has been documented as a potential side effect of steroid treatment, regardless of the route of administration (Dineen et al., 2019). Suppression with inhaled, topical or intra-articular steroids can occur; however, it is more likely among individuals taking oral or intravenous GCs (Broersen et al., 2015; Woods et al., 2015). It is also probable that the variation in hair cortisone and cortisol levels in GC users was influenced not only by route of administration, but also by duration of treatment, dosage and the disease for which the drug was prescribed (Broersen et al., 2015; Gow et al., 2011). Whether a steroid medication causes a reduction in endogenous GC levels, is dependent on the dose/potency of the steroid (LaRochelle et al., 1993; Van Staa et al., 2000), and on the duration of usage to a lesser extent (Schlaghecke et al., 1992; Henzen et al., 2000).The timing of GC dosing may also be of significance (Plat et al., 1999). All of these aspects are particularly relevant in an older population where a comparatively high prevalence of GC use is expected owing to an increase in morbidity. Moreover, GC pharmacodynamics and pharmacokinetics likely differ in an older population, owing to polypharmacy, changes in drug metabolism and in HPA axis functioning. The enzymes 11β-hydroxysteroid dehydrogenase (HSD) Types 1 & 2 are centrally involved in the metabolism of GCs and thus play an important role in steroid action. The subtypes are tissue-specific in distribution/concentration. 11-beta HSD2 converts cortisol to the inactive metabolite cortisone, and 11β-HSD1 mostly acts to reactivate cortisol from cortisone (Tomlinson et al., 2004). 11β-HSD1 activity appears to increase relative to HSD2 in aging (Chapman et al., 2013), and it seems that cortisol metabolism by this enzyme system can also be affected by steroid treatment. For example, Sherlock et al. (2015) found an increase in total cortisol metabolites and increased 11β-HSD1 activity in patients receiving oral hydrocortisone therapy for secondary adrenal insufficiency. It has also been asserted that conversion of cortisone back to cortisol at the tissue level drives the phenotype of glucocorticoid excess (Morgan et al., 2016).

The various mechanisms underlying the incorporation of steroid hormones into hair may be particularly important in explaining some of our findings. Raul et al. have suggested possible mechanisms for this include passive diffusion from blood into the hair follicle in development, from bodily secretion during formation of the hair shaft, and from external sources once the hair shaft has been formed (Raul et al., 2004). In keeping with this the results observed with users of topical GCs may thus be explained by participants directly applying hydrocortisone treatment directly on the scalp or by indirect transmission from the treated area elsewhere on the skin to the hair/scalp.

Our study has several strengths including a large population-based sample of older adults, measurement of both cortisol and cortisone, disaggregation by route of administration and measurement of covariates. There are also limitations which must be acknowledged. We didn't have information on the exact steroid being taken, the dosage or duration of use and we relied on self-reporting of GC medication use. It is possible that the latter will lead to under-reporting. However, drug prescription information can also be imperfect due to the potential for non-compliance, and additional use of over-the-counter medications. We also did not record use of mineralocorticoids or other drugs which may also influence HPA axis function.

5. Conclusions

We found that in older adults the use of systemic glucocorticoids is associated with a decreased hair concentration of cortisone. Meanwhile, hair cortisol was increased in individuals using local GC medicationsm, with further analysis revealing that this was most likely due to topical steroid use. We advocate that future hair cortisol/cortisone research studies should account for the confounding effect of GC medication use in their analyses, either by including steroid medication use as a covariate, or by excluding steroid users from the analyses outright. However, it is our belief that this would have to be decided on a study

by study basis, with consideration to the nature of the particular sample, the sample size and the particular research question(s) being addressed.

Declarations of Competing Interest

None.

CRediT authorship contribution statement

Viveka Guzman: Formal analysis, Writing - original draft. **Rose Anne Kenny:** Resources, Supervision, Writing - review & editing, Funding acquisition. **Joanne Feeney:** Conceptualization, Methodology, Investigation, Writing - review & editing.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.psyneuen.2020.104701.

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