ABSTRACT

Introduction
There are few studies on effects of ageing and gender on cortisol levels. Some studies demonstrate increased basal cortisol in older aged healthy subjects particularly higher levels in women.

Methods
All serum cortisol tests (n=35,802) performed from 2001 to 2012 were extracted. Results are reviewed by a Pathologist and history of medications (inhaled, oral, joint steroid) or HPA-axis disease annotated to results. After exclusions for history/medications (n=32) or missing data (1,830) including time of collection, 33,362 records were partitioned into 5 year age bands and then median, standard deviation and 2.5 and 97.5 centiles were determined for age group. Cortisol was analysed in 15 min time bands with a minimum of 100 records from 7.15 am to 5.30 pm and the median, 2.5 and 97.5 centile graphed.

Results
The population included 64.3 % women (mean age 44.9 years) and 35.7% men (mean age 47.5 years). Median cortisol was slightly higher in women (351 nmol/L) than men (337 nmol/L). Median cortisol rose throughout puberty and peaked in the 15-25 year age bands initially before a decrease and plateau in those aged between 30-60 years of age. The nadir median cortisol was 325 nmol/L at ages 35-40 years. Thereafter median cortisol rose steadily by ~ 160 nmol/L to reach the maximum median levels of 488 nmol/L in the oldest subjects (p<0.001), Examining the span of ages and trends in males and female separately where median cortisol was > 350 nmol/L, women had higher cortisol than men.

Conclusion
Median serum cortisol varies significantly with age and gender across the day in a large population.

BACKGROUND

There have been a number of studies on the effects of ageing on cortisol levels but small sample size has often limited significance of findings (Seeman et al). Two studies utilising salivary cortisol have demonstrated an increase in basal cortisol in older aged healthy subjects (n=56) (Nicolson et al) and higher levels in women amongst older adults (n=440) (Seeman et al). Although serum or plasma cortisol is more widely used in the clinical setting, limited data is available on total cortisol changes with age. Van Cauter et al (n=177) found increased 517% plasma cortisol with increasing age with an age related increase in the acrophase in women only. (Van Cauter et al).

OBJECTIVE

In view of the importance of cortisol as an endocrine hormone and the relative paucity of information about factors affecting levels, this study aimed to assess changes in serum cortisol in a large population over a 12 year period. We assessed the effects of age and gender during the 12 year time frame.

METHODS

• We extracted data on all serum cortisol tests (n=35,802) performed from 1st January 2000 to 31st December 2011 at Western Diagnostic Pathology (WDP), Myaree, Western Australia. Of pathology referrals to WDP, 85% are from general (family) practice providers and 15% from specialists or from hospitals. 80% are from metropolitan areas and 20% from rural or remote settings. Western Australia has a predominately Caucasian population. All results were de-identified prior to further analysis. Since the study fits the criteria of an audit, institutional ethics approval and informed consent were not required.

• Annotation to the laboratory record of current medications or relevant medical conditions is made including any history obtained of inhaled, oral, intra-articular or topical steroids, high dose progestrone, intrathecal or oral opioid or history of hypothalamo-pituitary-adrenal disorders or other relevant history. Any history of medications including oral contraceptive or pregnancy leading to available on cortisol results. All cortisol results of ≥ 100 nmol/L were discussed with the referring doctor unless otherwise directed by the duty Pathologist.

• Exclusion criteria included any record with unknown gender, unknown date of birth (n = 93), no time of collection (n = 1,830), history of confounding medications or medical conditions (n = 517). The remaining cortisol results (n = 33,362) were partitioned into 5 year age bands, with those aged 95 years and older truncated into one band. The mean, median, standard deviation (SD) and 2.5 and 97.5 centiles were determined for each age group. 95% CI were calculated for four major 5 year age bands.

RESULTS

Demographics
Of the total 33,362 records available for analysis, 64.3% (n = 21,454) were female and 35.7% (n = 11,908) were males. The mean age of women was 44.9 years (16.9 SD) with men slightly older with mean age 47.5 (19.3 SD). Median cortisol (351 nmol/L) was ~ 14 nmol/L higher in women (2.5-97.5 centiles 25-845) than men with a median cortisol of 337 nmol/L (2.5-97.5 centiles 26-721).

Trends of collection
The majority of the data (97.4%) was collected between 7.15 am and 5.30 pm with 70.2% (23,439) being collected in the morning before 11.00 am. Cortisol was analysed in 15 min time bands where a minimum of 100 records where available from 7.15 am to 5.30 pm. (Figure 1A) Cortisol median demonstrated a morning rise peaking at 7.45-8.00 am with the downward trend reversing briefly at 11.45 am (18 nmol/L rise) and 1.15 pm (23 nmol/L rise).

Trends with age over time and age/gender over time

Median cortisol over time from 7.45 am until 11.00 am was analysed between younger (35-50 years) and older (≥ 75 years) groups (Figure 3). There was a trend for older people to have the highest median cortisol at most time points, with the largest separation between higher cortisol concentrations in the elderly compared to younger subjects, occurring with samples collected later in the day.

Trends with age and age/gender

Data was partitioned into 5 year age bands and median and 2.5 and 97.5 centile plotted for each age band. (Figure 2A) Median cortisol rose steadily through puberty and peaked in the 15-25 year age bands before a decrease and plateau in those aged between 30-60 years of age. The nadir median cortisol was 325 nmol/L at ages 35-40 years. Thereafter median cortisol rose steadily by ~ 160 nmol/L to reach the maximum median levels of 488 nmol/L in the oldest subjects (p<0.001). Examining the span of ages and trends in males and female separately (Figure 2B) there was a significant difference in median cortisol between males and females in the younger adults (< 35 years of age, p < 0.001) and the older adults (≥ 75 years of age, p<0.001) with females having the higher median cortisol in these age bands. Similarly, when median cortisol was > 350 nmol/L in an age/gender band, women had the higher median cortisol (p<0.001).

DISCUSSION

In this large study population we found significant variation in median serum cortisol with age and gender with older subjects having higher median cortisol than younger subjects and highest median cortisol occurring in older women.

Age and Gender. Our findings of higher cortisol levels with increasing age and in particular higher levels of cortisol in women with age support those of Van Cauter et al. who found a 20-50% increase in plasma cortisol with ageing and an increased acrophase in women in a carefully controlled study group of 177 subjects. They also found that with increasing age the timing of the acrophase advanced and the nocturnal nadir increased with resultant reduced amplitude of the diurnal rhythm. We found that median serum cortisol increased with age, rising ~ 160 nmol/L from the nadir level in 35-40 year olds to a peak in the elderly subjects (≥ 75 years old). A second lower peak of median cortisol occurred in 15-25 year olds, and when median cortisol was > 350 nmol/L women’s levels where always higher than men.

Two studies analysing salivary cortisol also support our findings. Nicolson et al demonstrated an increase in basal cortisol in older aged healthy subjects and Seeman et al reported that in younger adults, males had higher salivary cortisol levels, in contrast to older adults where females had the higher levels. Reasons for this distinct age and gender pattern are not clear however mechanisms suggested include that HPA resiliency may decline with age leading to a loss of decline in cortisol following response to challenges of the HPA axis. It is now known that the rate of recovery of the HPA axis from a stimulus is most likely a function of HPA deactivating or anti-inflammatory responsiveness increased in older women more than similar aged men in response to CRH challenge (Greenspan) or to a driving challenge (Seeman).

CONCLUSION

This study of a large population found a significant association between median serum cortisol and increasing age and female gender. This study illustrates the crucial effects of time of sampling on assessment of serum cortisol but also highlights the relevance of age and gender in interpretation of results.

References:
Effects of Gender and Age on the levels and circadian rhythmity of plasma cortisol. Van Cauter et al, JCEM, 1996; Vol 81, 7, 2469-2474.


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VARIATION OF SERUM CORTISOL WITH AGE AND GENDER

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Table 1. Cortisol levels with gender and age group

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<th>Age</th>
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<th>Female</th>
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