

Biological indicators for burnout: verification using salivary α -amylase activity, cortisol and chromogranin A concentration

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Abstract

With nurses as subjects (32 subjects in the burnout group and 32 in the non-burnout group), 3 types of biomarkers, namely daytime salivary α -amylase activity, cortisol and chromogranin A concentration were measured in order to verify the biological changes brought about by burnout. Samples were collected at 4 time periods (within 30 minutes of waking up, at the start of work, before lunch, and at the end of work). There was a decline in

the physiological activity of α -amylase from the time of waking up to the start of work, caused by burnout. In addition, the physiological concentration of cortisol was found to gradually decline from the time of waking up to the start of work, caused by burnout, and exhibiting a flattened profile. The above results suggest burnout as the likely cause of hypofunction of the sympathetic-adrenal-medullary axis and hypothalamic-pituitary-adrenal axis.

Key words : burnout, nurse, cortisol, amylase, chromogranin A

I. Introduction

Burnout is “prolonged response to chronic emotional and interpersonal stressors on the job, and is defined by the three dimensions of exhaustion, cynicism, and inefficacy”¹⁾. After Frudenberger applied the concept of burnout to exhaustion experienced by human service providers²⁾, studies on factors leading to burnout and various losses resulting from burnout have been conducted primarily with education, medical and welfare workers as

the target. It has been indicated that burnout is the source, not only of decline in work performance^{3, 4)} and negative effects on work such as long-term absence therefrom^{5, 6)}, but also of physical health problems^{7, 8)}.

In addition, burnout is known to cause chronic work-related stress. Living bodies react to stress through 2 channels, namely the sympathetic-adrenal-medullary axis (SAM axis) and the hypothalamic-pituitary-adrenal axis (HPA axis). Due to stress, the SAM axis secretes such catecholamines as adrenalin and noradrenalin from the adrenal medulla and sympathetic nerves via the hypothalamus, and the HPA axis secretes glucocorticoid from the

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adrenal cortex.

Thus, in recent years, salivary α -amylase (hereafter, amylase), cortisol, and chromogranin A have become the focus of attention. Cortisol is a type of glucocorticoid which is secreted from the adrenal cortex via the HPA axis. There are multiple papers verifying changes in cortisol secretion associated with burnout. However, while there are reports indicating an increase in cortisol secretion in the morning associated with burnout^{9, 10)}, there are also reports of a decrease thereof^{11, 12)}. Hence, it can be said that no consistent view on this matter has been presented thus far.

Amylase an autonomic marker as this enzyme's activity is influenced by protein secretion rate and salivary flow rate, controlled via sympathetic and parasympathetic activity, respectively. Only a few articles exist which verify the amylase activity changes resulting from burnout. There are reports indicating secretion decline thereof in males¹³⁾ and reports indicating no change in activity¹⁴⁾. As such, no consistent views exist in this regard, either.

Chromogranin A exists within a chromaffin granule and is a soluble protein which is secreted from the adrenal medulla and sympathetic nerve endings along with catecholamine, and is a useful protein for the functional assessment of the SAM axis. There are reports concerning the correlation of interpersonal conflicts or anxiety in the workplace to the increase in the secretion of chromogranin A from the late afternoon onward¹⁵⁾; however, no paper focusing on the relevance thereof regarding burnout has been presented thus far.

Wingenfeld et al.¹⁶⁾ state the following

as reasons for the lack of consistency in the verification results of the stress hormone secretory activity and concentration as a result of burnout: differences in the evaluation measure and diagnostic criteria, differences in the measurement method of stress hormones, and lack of uniformity in the background of the subjects, such as occupational category, and soon. As such, consistent results regarding the connection between burnout and salivary biomarkers such as amylase, cortisol and chromogranin A have not been attained thus far, and no reports have yet been presented verifying the changes in the 3 salivary biomarkers associated with burnout under the same conditions. Therefore, in this study, we aimed to verify the biological changes caused by burnout by tracking the in-day fluctuations of salivary amylase, cortisol and chromogranin A.

II. Material and Methods

1. Participants

Surveys and examinations were conducted on 250 consenting nurses working under a 3-shifts/day system at Iwate Medical University Hospital. The surveys and examinations were carried out between October 1, 2014 and September 30, 2015. Those who had consumed alcohol during the previous day, smokers, and those who had worked the nightshift on the previous day were excluded, leaving 64 eligible subjects (25.6%) whose samples were collected without any defects.

2. Measurements of burnout

Regarding burnout, evaluation was conducted based on the Japanese version of the Pines burnout scale¹⁷⁾. This self-completed

evaluation measure consisted of 21 items categorized under 3 subscales, i.e., “physical exhaustion,” “emotional exhaustion,” and “mental exhaustion,” and under each item, the subjects were required to indicate the experience frequency on a 7-step scale (1=none ~ 7=always). If the score from the prescribed calculation was 2.0 or over and under 3.0, the subjects were categorized as belonging to the “physically and mentally sound group.” If the score was 3.0 or over and under 4.0, they were categorized as belonging to the “group with burnout warning symptoms.” If over 4.0 or over and under 5.0, they were placed in the “burnout group.” If 5.0 or over, the subjects were classified as being in the “pathological group with a clinical depressive state of burnout”¹⁷⁾.

A 2-group comparison was conducted of the burnout group of 4.0 or over and non-burnout group of under 4.0, as was a 2-group comparison of the pre-burnout/burnout group of 3.0 or over and healthy group of under 3.0.

3. Saliva collection and assay

On a workday, saliva was collected 4 times (30 minutes after waking up [hereafter, after wakeup], at the start of work, before lunch and at the end of work). Samples were taken a total of 2 times within 1 week of the burnout evaluation with a dedicated sampling tool (Salimetrics LLC, Carlsbad) and were stored immediately at -80°C until the day of the analysis.

Salivary cortisol and chromogranin A concentration were measured using the enzyme immunoassay, and the salivary amylase activity was measured using the colorimetric method. After defrosting, the stored samples were centrifuged for

15 minutes at 3,000 rpm, and only the supernatant liquid was used for analysis. After using the enzyme immunoassay kit (Salimetrics LLC, Carlsbad; Yanaihara Institute Inc., Shizuoka), and measuring the absorbance with the microplate reader (Bio-Rad, California), the cortisol concentration (pmol/ml) and chromogranin A concentration (pmol/ml) were quantified with a standard curve. In order to reduce the measurement error, a replicated experiment was performed 2 times. The salivary amylase activity (KIU/L) was measured with a dedicated measurement monitor (Nipro Co., Osaka) and a dedicated chip. The dedicated chip contained alpha-2-Chloro-4-nitrophenyl-4-galactopyranosylmaltoside (Gal-G2-CNP), causing hydrolysis, generating 2-Chloro-4-nitrophenol (CNP). Changes in the reflected light intensity of the test paper by means of this CNP were observed with a monitor in order to measure the amylase activity¹⁸⁾.

4. Data analyses

The mean of the measured value for the 4 time periods (after wakeup, at the start of work, before lunch, at the end of work) taken over 2 days was used for analysis.

Because it is a known fact that individual differences exist in the basal secretion volume of stress hormones¹⁹⁾, in order to eliminate such effects in this study, the rate of change of biomarkers during the day in individuals was calculated, and a comparative examination was made between the 2 groups, namely the burnout group and non-burnout group, and the pre-burnout/burnout group and healthy group. The calculation method was rate of change $=(\text{start of work-after wakeup}) / \text{after wakeup} \times 100$, rate of change $=(\text{before lunch} - \text{start of$

Table 1. Background of study participants

Characteristics	Overall	Burnout group	Non-burnout group	p
Gender				
Male	6 (9.4%)	4 (12.5%)	2 (6.2%)	0.336
Female	58 (90.6%)	28 (87.5%)	30 (93.8%)	
Age	35.8 ± 10.4	32.5 ± 8.3	39.2 ± 11.3	0.015*
No. of years employed				
5 year division				
Under 5 years	18 (28.2%)	12 (37.5%)	6 (18.8%)	0.095
5 years or more	44 (71.8%)	20 (62.5%)	26 (81.2%)	
10 year division				
Under 10 years	31 (48.4%)	19 (59.4%)	12 (37.5%)	0.080
10 years or more	33 (51.6%)	13 (40.6%)	20 (62.5%)	

Data are given as means and standard deviations or numbers and percentages.

*p<0.05

Table 2. Secretion concentration and activity of salivary amylase, cortisol and chromogranin A in the burnout group and non-burnout group.

Factors	Burnout group	Non-burnout group	p	Correlation between burnout score	
				p	r
Amylase (KIU/L)					
After wakeup	73.6 (49.4)	72.1 (42.6)	0.989	0.912	-0.014
At the start of work	103.1 (77.9)	129.9 (81.3)	0.087	0.460	-0.094
Before lunch	105.6 (59.3)	117.2 (55.1)	0.298	0.716	-0.046
At the end of work	114.0 (55.0)	119.7 (61.8)	0.722	0.929	0.011
Cortisol (pmol/mL)					
After wakeup	15.7 (8.1)	18.1 (8.1)	0.184	0.269	-0.140
At the start of work	17.2 (10.5)	13.3 (5.6)	0.327	0.416	0.104
Before lunch	7.3 (6.6)	5.9 (1.8)	0.825	0.835	0.027
At the end of work	5.4 (4.2)	4.7 (2.0)	0.515	0.789	0.034
Chromogranin A (pmol/mL)					
After wakeup	32.9 (15.9)	28.0 (16.1)	0.225	0.644	0.059
At the start of work	38.5 (16.3)	37.2 (17.1)	0.748	0.714	0.047
Before lunch	28.8 (14.4)	24.8 (11.3)	0.217	0.394	0.108
At the end of work	31.4 (15.0)	28.6 (12.8)	0.420	0.276	0.138

Data are given as means and standard deviations.

work) / start of work × 100, rate of change = (end of work-before lunch) / before lunch × 100

Regarding the interval/ratio scale, Shapiro-Wilk's normality test was used, and Mann-Whitney's U test, and the t test were used to

determine statistical differences. In addition, the results of the interval/ratio scale were expressed as the mean and standard error. The χ^2 test or Fisher's exact test was used for the nominal scale.

Furthermore, a correlation analysis for the

Table 3. Rate of change in salivary amylase, cortisol and chromogranin A in the burnout group and non-burnout group

Factors	Burnout group	Non-burnout group	p
Amylase rate of change (%)			
After wakeup-start of work	56.3 (96.2)	114.5 (128.0)	0.044*
Start of work-before lunch	24.7 (61.9)	4.5 (43.7)	0.280
Before lunch-end of work	16.2 (34.1)	5.3 (32.0)	0.220
Cortisol rate of change (%)			
After wakeup-start of work	26.3 (77.0)	-11.7 (54.6)	0.048*
Start of work-before lunch	-50.6 (27.1)	-51.2 (19.7)	0.537
Before lunch-end of work	-16.5 (36.0)	-16.9 (35.2)	0.957
Chromogranin A rate of change (%)			
After wakeup-start of work	45.7 (104.1)	91.4 (204.2)	0.460
Start of work-before lunch	-6.5 (98.8)	-4.9 (119.4)	0.979
Before lunch-end of work	34.7 (122.1)	56.1 (173.9)	0.883

Data are given as means and standard deviations.

The rate of change is the rate of increase between the 2 adjacent time frames. For example, after wakeup-start of work is calculated as (start of work-after wakeup) / after wakeup \times 100.

*p<0.05

3 salivary stress biomarkers for all samples and a correlation analysis of the burnout score and biomarkers for each of the 4 time periods were conducted. For each item, the Shapiro-Wilk normality test was carried out, and for the correlation analysis, Pearson's correlation coefficient or Spearman's rank correlation coefficient was used. Moreover, a single regression analysis was conducted for the 3 salivary biomarkers. SPSS 22.0J for Windows (IBM, New York) was used for statistical processing, and the significance level for all statistical analysis was less than 5%.

5. Ethical considerations

Personally identifiable data was excluded, and the protection of personal information was considered in managing and processing data. This study has also received the approval of the Ethics Committee of Iwate Medical University School of Medicine (H26-65).

III. Results

1. Study Participants

The burnout group consisted of 32 subjects (4 men, 28 women) and the non-burnout group of 32 subjects (2 men, 30 women). The average age of the burnout subjects was 32.5 years (S.D.=8.3), and 39.2 years for non-burnout subjects (S.D.=11.3), with a significant difference ($p=0.015$) observed between the 2 groups. Since shortness in the length of employment has been suggested as a factor related to burnout^{20, 21}, in this study, a division has been made according to the length of employment (5 year and 10 year division). In the burnout group, the subjects tended to be employed for only a short term ($p=0.095$, $p=0.080$, respectively), and no significant difference was observed (Table 1).

2. Relevance between the 3 types of salivary biomarkers and burnout

Table 2 shows the amylase activity, cortisol

Table 4. Background and rate of change in salivary amylase cortisol, chromogranin A for the pre-burnout/burnout group and healthy group

Factors	Pre-burnout/burnout group	Healthy group	p
Gender			
Male	4 (8.2%)	2 (13.3%)	0.432
Female	45 (91.8%)	13 (86.7%)	
Age	34.7 (9.9%)	37.9 (11.2%)	0.306
No. of years employed			
5 year division			
Under 5 years	14 (28.6%)	4 (26.7%)	0.583
5 years or more	35 (71.4%)	11 (73.3%)	
10 year division			
Under 10 years	24 (49.0%)	7 (46.7%)	0.875
10 years or more	25 (51.0%)	8 (53.3%)	
Amylase rate of change (%)			
After wakeup-start of work	87.1 ± 123.6	79.7 ± 91.1	0.686
Start of work-before lunch	17.2 ± 55.4	6.1 ± 50.8	0.396
Before lunch-end of work	11.1 ± 35.5	9.6 ± 25.5	0.877
Cortisol rate of change (%)			
After wakeup-start of work	9.44 ± 72.0	0.28 ± 59.6	0.794
Start of work-before lunch	-49.5 ± 25.4	-55.6 ± 15.9	0.782
Before lunch-end of work	-20.2 ± 32.2	-5.4 ± 43.4	0.170
Chromogranin A rate of change (%)			
After wakeup-start of work	67.7 ± 146.2	71.1 ± 212.9	0.379
Start of work-before lunch	-12.1 ± 85.9	15.2 ± 165.2	0.769
Before lunch-end of work	58.3 ± 166.1	3.3 ± 58.2	0.202

Data are given as means and standard deviations or numbers and percentages.

and chromogranin A concentration measured 4 times during the day after wakeup, at start of work, before lunch and at the end of work. As a result of verifying the correlation between the burnout score and each biomarker measurement value, no significant item was observed. Next, as a result of comparing the 2 groups, namely the burnout and non-burnout groups, there was a tendency for salivary amylase activity after wakeup to be reduced in the burnout group (burnout group 103.1 ± 77.9 , non-burnout group 129.9 ± 81.3 , $p=0.087$), but there was no item with a significant difference for each measured time period for any of the 3 salivary biomarkers.

Table 3 shows the inter-group comparison between the burnout group and non-burnout group regarding the biomarker rate of change to eliminate individual differences in the basal secretion volume of stress hormones. As a result of the analysis, the amylase rate of change was low in the burnout group during the period from wakeup to the start of work. (Burnout group, non-burnout group: average rate of change \pm S.D.; rate of change 56.3 ± 96.2 , 114.5 ± 128.0 , $p=0.044$). Additionally, there is generally a physiological concentration decline in cortisol from the time of wakeup to the start of work; however, in the burnout group, a decline in concentration was not

observed, but a significant difference in the rate of change was observed (rate of change 26.3 ± 77.0 , -11.7 ± 54.6 , $p=0.048$). With regard to chromogranin A, no item with a significant difference was found.

3. Correlation between the population including pre-burnout and salivary biomarkers

Biological changes in those in a burnout state were verified, and examinations were made to see whether there were any items with significant differences when the pre-burnout group was included. A comparison was made in the average rate of change for the 3 salivary biomarkers between the pre-burnout /burnout group with a burnout score of 3 points or higher (49 subjects) and the healthy group with a score of under 3 points (15 subjects); however, no item with a significant difference was observed (Table 4).

IV. Discussion

In this study, biological changes resulting from burnout were verified through 3 salivary biomarkers, namely salivary amylase, cortisol and chromogranin A.

The subjects of this study were nurses. The workplace of nurses is directly linked to life and death situations, and it is thought that such an environment contributes to the development of a feeling of insufficiency and problems with interpersonal relationship with coworkers²²⁾. In addition, the 3-shift work system results in an increased workload, aggravated by irregular work hours and overwork. Thus, the nursing profession is one in which burnout is extremely probable²³⁾. In prior studies, lack of experience and the accompanying lack of ability to cope also

have been suggested as factors leading to burnout^{20,21)}. In this study, the burnout group were younger in age, and although there was no significant difference, their years of employment tended to be shorter. In this analysis, taking into consideration the selection bias of the samples, age adjustment between the groups was intentionally not made. Due to the fact that changes in salivary cortisol and salivary amylase concentration change very slightly with age²⁴⁻²⁶⁾, it is thought that age difference in this study had little impact on the measurement values of salivary stress hormones.

No significant difference was found in the comparison of salivary stress biomarkers at the 4 time periods and no observations were made other than the downward trend in the salivary amylase after wakeup among those of the burnout group ($p=0.087$). A factor contributing to this may be differences in the individual basal secretion volume for the 3 stress biomarkers.

All 3 salivary biomarkers are subject to in-day fluctuation. With cortisol, the in-day changes can be measured. For example, one method involves multiple collection of saliva within 1 hour of waking up, with the secretion quantity and trend evaluated during that time (cortisol awakening response). Another method involves the collection of saliva 4 ~ 8 times from morning to evening and evaluating the total secretion quantity during the day (daily output). There is also a method of collecting saliva in the morning and at night and evaluating the trend in the secretion quantity (diurnal slope)²⁷⁾. In this study, saliva was collected only once at the time of wakeup and collection was not made at night time. Instead,

the unique method was employed, that of calculating the rate of change from wakeup to the start of work, from the start of work to before lunch, and from before lunch to the end of work, and individual in-day fluctuations were evaluated while eliminating individual differences in the basal secretion volume. As a result, it was clarified that significant changes attributed to burnout occur in salivary amylase activity and cortisol concentration rate of change from wakeup to the start of work.

Salivary amylase is generally the lowest in the morning, and increases throughout the day²⁸⁾. Both the burnout group and non-burnout group manifested similar in-day fluctuations, but in the burnout group the rate of increase from wakeup to the start of work was significantly lower. This result indicates the possibility of the hypofunction of the SAM axis attributed to burnout.

Salivary cortisol normally reaches a peak 30 minutes after wakeup, and declines as the day progresses. Dmitrieva et al.²⁹⁾ stated that there are individual differences in the in-day fluctuations of cortisol and presented 3 patterns, namely a normative profile, elevated profile and flattened profile. According to their report, in the healthy group, 73% corresponded to the normative profile, where the secretion quantity rapidly increases for 30 minutes from wakeup, gradually declining during the course of the day, and manifesting low secretion at bedtime similar to wakeup time. 20% corresponded to the elevated profile, with high secretion after wakeup, and comparatively gradual increase up to 30 minutes thereafter. In comparison to the other 2 patterns, the secretion quantity at

bedtime was high. Only 7% corresponded to the flattened profile, in which little change was seen in the 30 minutes from wakeup. Compared to the other patterns, the rate of decline during the morning was low. This is thought to indicate hypoactive HPA-activation, a condition manifested in chronic fatigue syndrome (CFS)³⁰⁾, impaired metabolic health³¹⁻³³⁾, and soon. Hypoactive HPA-activation is a state of the HPA axis adapting excessively to stress. The number of glucocorticoid receptors decreases, causing a decline in cortisol synthesis. In addition, because there is a heightened sensitivity to cortisol, cortisol after wakeup is low and the decline during the day is also gradual³⁴⁾. When the study results herein are applied to the 3 classifications, the non-burnout group corresponds to the normative profile. The burnout group, on the other hand, does not have high secretion quantity after wakeup and does not show signs of decrease in secretion at the start of work; therefore, it can be regarded as having the same in-day fluctuation as the flattened profile.

Burnout is defined from 3 aspects, namely "emotional exhaustion," "depersonalization," and "decline in personal accomplishment." There are various evaluation methods for burnout; however, according to Tao et al., Pines Burnout Measure is reputed to be most suited to assessing emotional exhaustion among other burnout aspects³⁵⁾. There have been other past reports on the common factors of emotional exhaustion and chronic fatigue syndrome, focusing particularly on the HPA axis³⁶⁻³⁸⁾. The results of this study also suggests the possibility of burnout, particularly emotional exhaustion, being the cause of

hypofunction of the HPA axis and SAM axis.

Furthermore, in this study, we could not verify the relevance between chromogranin A and burnout. According to the in-day fluctuation of chromogranin A, the level of secretion is low during the entire day, but begins to rise at night (10:30 p.m.), reaching a peak at wakeup (7:00 a.m.), and reaching a low 1 hour afterwards (8:00 a.m.)³⁹⁾. In other words, the time from the peak to the lowest level of chromogranin A is 1 hour, which is extremely short in comparison to that for cortisol. Thus, according to the method of saliva collection after wakeup and at start of work employed in this study, the peak and lowest value could not be distinguished, so it is possible that there was a significant difference that could not be observed.

This study had limitations. The first factor relates to the participants. The samples obtained were of a limited number, specifically 32 from each group, and there is a gender difference in the hormone secretion quantity. For example, the rate of salivary cortisol increase is higher in females than in males⁴⁰⁾, there is greater secretion of salivary amylase in females than males in the late afternoon¹⁴⁾, and the secretion quantity of salivary chromogranin A differs according to the menstrual cycle⁴¹⁾. The second factor has to do with the timing of sample collection. In-day fluctuations of salivary chromogranin A were explained above, and the secretion quantity of salivary cortisol was also seen to rise from wakeup, reaching its peak 15-30 minutes thereafter¹⁰⁾. Samples from study participants were collected within 30 minutes of wakeup; however, there is a possibility that the peak secretion time was missed.

In addition, the work environment for the start of work, before lunch, and the end of work differ, and there is approximately up to a 1-hour discrepancy for each of the time periods. Regarding this matter, the objective of this study was to verify whether salivary biomarkers are effective as an easy and feasible burnout screening tool, and therefore, collection was not carried out within a strict time frame but in a workable time frame under normal work conditions.

The third factor involves external factors which affect hormone secretion. It is known that reduced hours of sleep or lower sleep quality results in the decrease in cortisol secretion at wakeup⁴²⁾; thus, investigation into the state of sleep should also have been considered.

In this study, biological changes caused by burnout were verified using 3 salivary biomarkers. By observing the results derived from salivary amylase and cortisol, there is a possibility that the activities of the SAM axis and HPA axis were suppressed due to burnout. In addition, it is noteworthy that by using an analysis method of individual in-day rate of change, the possibility of discerning biological changes caused by burnout from just 2 time periods, namely at wakeup and the start of work, was opened up.

By means of this study, the possibility of making salivary amylase and cortisol calculation measurements a burnout biomarker was established. However, when pre-burnout subjects were included, no biological changes between them and healthy subjects could be observed. Thus, in order to apply and develop this method as a screening tool, it is thought that continued verifications

including that of measurement methods need to be implemented.

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バーンアウトの生物学的指標：
唾液 α - アミラーゼ活性, コルチゾール,
クロモグラニン A 濃度を用いた検証

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要旨

看護師を対象 (バーンアウト群 32 名, 非バーンアウト群 32 名) として日中の唾液 α - アミラーゼ活性, コルチゾール, クロモグラニン A 濃度の 3 種類のバイオマーカーを計測し, バーンアウトがもたらす生物学的变化を検証した. 起床後 30 分以内, 勤務開始時, 昼食前, 勤務終了後の 4 点で検体採取し, ストレスホルモンの基礎分泌量の個体差を排除する目的でバイオマーカー変化率を算出し解析した結果, 唾液 α - ア

ミラーゼにおいて, 起床時から勤務開始前にかけての生理的活性増加はバーンアウトにより減弱していた. また唾液コルチゾールは起床時から勤務開始前にかけての生理的濃度低下がバーンアウトにより減弱し, flattened profile を呈した. 以上の結果よりバーンアウトが sympathetic-adrenal-medullary axis および hypothalamic-pituitary-adrenal axis の機能低下をもたらしている可能性が示唆された.

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