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## Salivary cortisol day profiles in elderly with mild cognitive impairment

Oliver T. Wolf<sup>a, c</sup>, Antonio Convit<sup>a, b,\*</sup>, Elissa Thorn<sup>a</sup>, Mony J. de Leon<sup>a, b</sup>

<sup>a</sup> Center for Brain Health, Neuroimaging Laboratory, New York University School of Medicine, 560 First Avenue, New York, NY 10016, USA

<sup>b</sup> Nathan Kline Institute for Psychiatric Research, Orangeburg, NY, USA

<sup>c</sup> Institute of Experimental Psychology II, University of Düsseldorf, Düsseldorf, Germany

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### Abstract

It is unknown whether hypothalamus–pituitary–adrenal (HPA) axis dysfunction is associated with the memory impairments observed among elderly participants with mild cognitive impairment (MCI), a group considered at increased risk for Alzheimer’s disease (AD). Therefore, salivary cortisol levels were measured at six points over the course of the day while at-home in MCI participants ( $n=16$ ), normal elderly ( $n=28$ ), and young controls ( $n=14$ ). Results revealed that MCI participants did not show elevated salivary cortisol levels. The 9 a.m. cortisol level of the MCI group was significantly lower than the 9 a.m. level of the young controls, but did not differ from those of the normal elderly group. In contrast to the other two groups, within the MCI group mean cortisol levels were inversely related to immediate recall of paragraphs. No association was observed between mean cortisol levels and performance in paired associates and digit span. Whether cortisol levels, in conjunction with other factors, such as hippocampal volume, will lead to improved prediction of future decline to AD in participants with MCI remains to be established in longitudinal studies. © 2002 Elsevier Science Ltd. All rights reserved.

*Keywords:* Mild cognitive impairment; Alzheimer’s disease; Hippocampus; Cortisol; Memory

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\* Corresponding author. Tel.: +1-212-263-7565; fax: +1-212-263-3270.  
E-mail address: antonio.convit@med.nyu.edu (A. Convit).

## 1. Introduction

Elderly individuals demonstrating mild cognitive impairments (MCI) have recently been the focus of renewed attention (Petersen et al. 1999, 2001; Ritchie et al., 2001; Hogan and McKeith, 2001). However, there is currently no uniform definition of what constitutes such an individual (Hogan and McKeith, 2001). Our laboratory has chosen to define MCI functionally using the Global Deterioration Scale [GDS](Reisberg et al., 1988). A GDS score is assigned after an interview with the participant and care-giver/spouse by a trained clinician utilizing clearly operationalized criteria. Individuals with MCI receive a GDS score of 3 (see Methods for details) and generally have subjective memory complaints and may have mild word-finding difficulties and/or decreased performance in demanding employment situations. Although performance on cognitive testing is not used to define MCI, participants with MCI have memory deficits on formal neuropsychological testing. Individuals with MCI do not have difficulties with basic activities of daily living, and by definition do not meet DSM IV diagnostic criteria for dementia of the Alzheimer's type (AD).

Longitudinal prediction studies have demonstrated that elderly participants with MCI are at increased risk for Alzheimer's disease (Flicker et al., 1991; Petersen et al., 2001; Morris et al., 2001). Neuroimaging studies have observed that MCI participants have qualitative hippocampal atrophy (de Leon et al., 1997a) as well as reductions in hippocampal volume (Convit et al., 1997; Jack et al., 1997) and metabolism (De Santi et al., 2001). Moreover, hippocampal atrophy predicts future decline to AD among elderly with MCI (de Leon et al., 1993; Jack et al., 1999).

The hippocampus, in addition to being essential for declarative memory formation (Squire, 1992), is also critically involved in the feedback regulation of cortisol secretion through its regulation of the Hypothalamus–Pituitary–Adrenal (HPA) axis (Jacobson and Sapolsky, 1991). Elevated endogenous cortisol levels are associated with poorer declarative memory and/or hippocampal atrophy in aging (O'Brien et al., 1994; Seeman et al., 1997; Lupien et al., 1998), AD (de Leon et al., 1988; Oxenkrug et al., 1989; O'Brien et al., 1996), Cushing's disease (Starkman et al. 1992, 1999), depression (Rubinow et al., 1984), and Schizophrenia (Walder et al., 2000). In line with these clinical findings there are experimental studies showing that exogenous cortisol administration impairs declarative memory (Kirschbaum et al., 1996; Wolkowitz et al., 1990; Lupien and McEwen, 1997; Newcomer et al., 1999; Wolf et al., 2001) and reduces hippocampal glucose metabolism (de Leon et al., 1997b).

Subtle increases in cortisol secretion occur during normal aging, which are especially pronounced in the evening (Dodt et al., 1994; Van Cauter et al., 1996; Kern et al., 1996). However, there is an increased variance within older subjects and longitudinal studies have revealed that cortisol levels remain stable in a certain portion of older adults over the time of three to six years (Lupien et al. 1994, 1996). Patients with AD have higher basal and/or post Dexamethasone (Dex) cortisol levels than healthy elderly participants in several (e.g. Davis et al., 1986; Maeda et al., 1991; O'Brien et al., 1996; Hartmann et al., 1997; Swanwick et al., 1998; Umegaki

et al., 2000), but not all (e.g. Dodt et al., 1991; Carlson et al., 1999) studies. Moreover AD patients show reduced central and peripheral glucocorticoid sensitivity (Linder et al., 1993; Nijhuis et al., 1994; de Leon et al., 1997b). Little is known about neuroendocrine alterations among elderly individuals with MCI. The present study was designed to investigate whether salivary cortisol levels are elevated among participants with MCI, a group that has previously been shown to have hippocampal atrophy and be at increased risk for future AD. The measurement of ambulatory salivary cortisol over the course of the day has been proven fruitful in multiple studies investigating psychiatric (e.g. Goodyer et al., 1996; Harris et al., 2000), endocrine (e.g. Raff et al., 1998; Castro et al., 1999), or psychosocial (e.g. Ockenfels et al., 1995; van Eck et al., 1996; Vedhara et al., 1999) conditions.

## 2. Methods and materials

Fourteen young normal participants (YN), 28 normal elderly participants (NE), and 16 elderly participants with mild cognitive impairment (MCI) participated in this study. Participants were community-residing volunteers taking part in ongoing studies of normal aging and dementia at our university-based Center for Brain Health and Alzheimer's Disease Core Center. Participants represent a typical research clinic population and are not drawn randomly from the general population. They are volunteers responding to publicity about the research program, spouses of the demented patients being evaluated in our clinic, individuals with concerns about their memory, or they are referred by physicians. Young participants were recruited through a web-based posting at two local universities student sites. Please refer to Table 1 for socio-

Table 1  
Socio-demographic and neuropsychological characteristics of the participants<sup>a</sup>

	YN ( <i>n</i> =14)	NE ( <i>n</i> =28)	MCI ( <i>n</i> =16)
Gender (M/F)	11/3	16/12	12/4
Age	27.0±2.1	68.6±1.2 <sup>b</sup>	70.9±2.0 <sup>b</sup>
MMSE	29.7±0.2	29.1±0.2	28.3±0.4 <sup>b</sup>
Education	16.0±0.6	16.0±0.4	14.7±0.7
PRI	7.2±0.5	4.4±0.5 <sup>b</sup>	4.6±0.7 <sup>b</sup>
PRD	8.1±0.5	5.4±0.5 <sup>b</sup>	4.8±0.8 <sup>b</sup>
PAI	6.7±0.8	7.3±0.5	5.3±0.6
PAD	10.5±1.0	8.1±0.5 <sup>b</sup>	5.9±0.8 <sup>b,c</sup>
DSF	7.6±0.3	7.3±0.3	7.1±0.2
DSB	6.1±0.2	5.6±0.3	4.6±0.3 <sup>b,c</sup>

<sup>a</sup> YN: Young control group; NE: Normal elderly group; MCI: mild cognitive impairment group. MMSE: Mini mental status examination; PRI: paragraph recall, immediate recall; PRD: paragraph recall, delayed recall; PAI: paired associates, immediate recall; PAD: paired associates, delayed recall; DSF: digit span forward; DSB: digit span backward.

<sup>b</sup>  $p < 0.05$  compared to YN.

<sup>c</sup>  $p < 0.05$  compared to NE.

demographic and neuropsychological characteristics of the participants. The study was approved by the Institutional Review Board and all participants gave informed written consent. Participants underwent a thorough medical, neurological, psychiatric, and neuropsychological screening protocol. Individuals with any DSMIV Axis I psychiatric diagnosis, history of head trauma with loss of consciousness, or history of steroid use during the previous 6 months were excluded. In addition, MRIs were obtained to rule out lesions. Although we do not exclude non native-English speakers, we do exclude individuals whose proficiency in English could affect the results of the neuropsychological assessment. The diagnosis of MCI was established by functional staging utilizing the Global Deterioration Scale [GDS] (Reisberg et al., 1988); MCI participants receive a score of 3 and normal participants receive a score of 1 or 2 depending on whether on questioning they report their memory to be as good as it once was. A GDS score of 3 is similar to a rating of 0.5 on the Clinical Dementia Rating (CDR). Elderly individuals with MCI have no impediments in basic activities of daily living but may have slightly reduced MMSE scores.

In addition to the GDS and the Mini Mental Status Examination (MMSE), subtests from the Wechsler Memory Scale Revised (paired associates and digit span; Wechsler, 1987) and the Guild Memory test (paragraph recall; Gilbert and Levee, 1971) were administered. The clinical assessments as well as the cognitive testing were performed as part of the biannual clinical evaluations of the subjects and was within three months of the day of the salivary collection.

### *2.1. Saliva sampling*

Participants collected the saliva samples themselves, while at home, using plain (without citric acid to stimulate saliva flow) polysterrolle Salivette collection devices (Sarstedt, Rommelsdorf, Germany). Samples were collected at 9 a.m., 11 a.m., 2 p.m., 4 p.m., 9 p.m., and 11 p.m. on a “typical” day for the subject. Participants were provided with a collection diary on which they entered the times of collection if they differed by more than 15 minutes from the recommended times. Days where there was an anticipated physical or psychological stress (e.g., sport or exam days) were avoided. Individuals were given clear written instructions and were asked to refrain from smoking or exercise for at least 30 minutes prior to collecting a sample. Participants were also instructed not to drink anything for at least five minutes prior to collection of samples. We had neglected to ask subjects to record their wake up time. Twenty seven subjects entered this information spontaneously onto the collection diary they were provided. Samples were sent to the laboratory by mail or delivered to the laboratory in person. The Salivettes were stored in a freezer until they were sent off for analysis to the Center for Psychobiological and Psychosomatic Research of the University of Trier, Germany, where one of the authors (OTW) had trained. The analysis of saliva free cortisol is quite robust; it has been shown previously that the unfrozen shipment of Salivettes does not influence the results (Clements and Parker, 1998).

## 2.2. *Free cortisol analysis*

Salivary cortisol levels were determined by a time-resolved immunoassay with fluorometric detection, as described in detail elsewhere (Dressendorfer et al., 1992). Inter- and intra-assay coefficients of variance were below 10%.

## 2.3. *Statistical analysis*

The demographic and cognitive data were analyzed using an Analysis of Variance (ANOVA) with diagnosis (YN, NE, and MCI) as the grouping factor. We first assessed whether elderly participants with MCI had elevated cortisol values using an ANOVA, with diagnosis (NE-MCI) as the grouping factor. In a second analysis the two elderly groups were compared with the young control group (YN), again using an ANOVA. Since few females were in the YN and MCI group, additional analyses were performed including only males. When appropriate, all reported results were corrected with the Huynh Feldt procedure as the adjustment for multiple repeated measurements. Post hoc testing of significant results was done using the Tukey HSD test. In order to further characterize the circadian cortisol pattern, circadian cortisol slopes were computed for each of the three subject groups. This was done using linear regression predicting the natural logarithmic transformed cortisol levels with the time of day variable (see Stone et al., 2001).

In addition to the group comparisons, we also investigated in an exploratory fashion (without alpha correction for the multiple correlations performed) whether average daily cortisol levels (the sum of the six daily values divided by six) were associated with any of the cognitive measures (paired associates, paragraphs, and digits) within each of the three groups of subjects. This was done using Pearson's correlations. The use of an average cortisol measure was chosen in order to reduce the amount of correlations performed. Moreover prior studies in Cushing patients or healthy elderly subjects have observed associations between memory measures and averaged cortisol levels (Starkman et al., 1992; Lupien et al., 1998).

## 3. Results

### 3.1. *Demographic characteristics*

The three groups did not differ in years of formal education. Normal and mildly impaired elderly participants did not differ in age. The MMSE in participants with MCI was not different from normal elderly, but was significantly lower than for young participants. Moreover, MCI participants had lower performance on delayed recall of the paired associates and digit backwards than normal elderly participants (See Table 1). We had neglected to include a wake-up time in the diary that participants kept during the at-home saliva collections. About 50% of the participants provided that information spontaneously. Among those participants with this data,

on average, young participants ( $n=10$ ) awoke later (8:30 a.m. versus 7:45 a.m.) than old participants ( $n=17$ ).

### 3.2. Salivary day profiles

Elderly participants with and without MCI did not differ in their cortisol levels, as indicated by the absence of a significant MCI group main effect and an absence of a significant group by time interaction (both  $F < 1$ ,  $p > 0.30$ ). As expected a strong time main effect was observed ( $F(3.9, 164)=30.4$ ,  $p < 0.001$ ); cortisol levels for the first four time points declined significantly from one measurement to the next, with the highest level being the first morning value. When the young control group was included in the group ANOVA, again there was no main group effect ( $F < 1$ ,  $p > 0.30$ ) and again there was a significant time effect ( $F(4.2, 232.8)=53.7$ ,  $p < 0.001$ ). However, when the YN group was included in the analysis there was a significant group by time interaction ( $F(8.5, 232.8)=1.95$ ,  $p < 0.05$ ). Post hoc testing revealed that MCI subjects had significantly lower cortisol levels than the YN in the morning at 9 a.m., while no significant difference existed between the MCI group and the elderly control group. No additional differences were observed between the three groups for any of the other five time points (see Fig. 1). Almost identical results were obtained, when the analyses were performed utilizing the data from the men only, except that the group by time interaction for the comparison between all three groups became a non-significant trend ( $p=0.07$ ). In order to investigate whether the later wake up time of the young group could account for the observed higher 9 a.m. cortisol levels an additional correlational analysis was performed for those 27 subjects for which wake

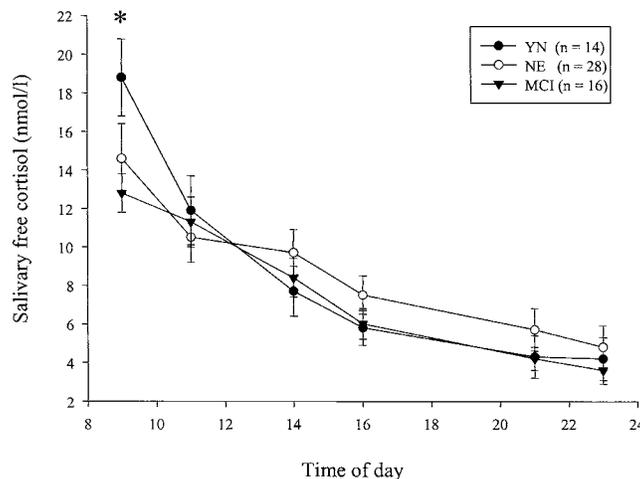


Fig. 1. Salivary cortisol levels in healthy young subjects, healthy elderly subjects and subjects with mild cognitive impairment. (Error bars represent standard error of means.) \*,  $p < 0.05$  (Tukey post hoc test) between healthy young subjects and subjects with mild cognitive impairment

up time information had been obtained. However, the correlation between wake up time and 9 a.m. cortisol was not significant ( $r=0.13$ ).

We also computed the cortisol slopes for the three groups. The slope values were (Mean $\pm$ SE; YN:  $-0.115\pm 0.014$ ; NE:  $-0.087\pm 0.008$ ; MI:  $-0.100\pm 0.009$ ), which were within the “typical range” previously reported (Stone et al., 2001). An ANOVA indicated that the three groups did not differ in their cortisol slopes ( $F(2, 55)=1.93$ ,  $p=0.16$ ).

Average cortisol levels were not associated with cognitive test performance in young subjects or normal elderly subjects. However, among subjects with MCI, average cortisol levels were inversely correlated with immediate recall of the paragraphs ( $r=-0.55$ ,  $p<0.05$ ; see Fig. 2(a)), and although non significantly, were also inversely correlated with the delayed recall of the paragraphs ( $r=-0.38$ ,  $p=0.15$ ; see Fig. 2(b)).

#### 4. Discussion

To the best of our knowledge this is the first report on cortisol levels in a group of elderly participants with MCI. We had speculated that participants with MCI, who as a group have hippocampal atrophy and impaired hippocampal function (Convit et al., 1997; Jack et al., 1997; De Santi et al., 2001), may also have impaired hippocampal-based cortisol feedback inhibition and thus show increased free salivary cortisol levels. Our results indicate that normal and mildly impaired elderly participants do not differ in their salivary cortisol levels over the course of the day. The cortisol slopes also did not differ between the groups. However, due to the small sample size this negative finding could reflect a lack of power of the current study. While ambulatory saliva sampling allows the assessment of cortisol in the typical living environment of the subject, it does not allow control for potential influencing variables like activity, diet etc. Therefore, it is possible that cortisol levels sampled in a standardized laboratory setting might have revealed different results. Moreover, age-associated alterations in basal cortisol levels are most pronounced during nighttime (Van Cauter et al., 1996), a time only partly covered by our sampling protocol, although the 11 p.m. sample should have been close to the daily cortisol nadir. It also remains to be established whether individuals with MCI have adequate feedback control of their HPA axis. In order to assess feedback control we plan endocrine challenge tests such as the Dexamethasone/CRH test (Heuser et al., 1994; Kudielka et al., 1999) in this group.

Individuals with MCI are at an increased risk of future development of AD, but the category of MCI is not homogenous. The annual conversion rate estimated from multiple studies ranges from 6–25% (Petersen et al., 2001), indicating that a large portion of MCI participants do not go on to develop AD within short periods of time. Moreover 75% (but not 100%) of MCI participants show signs of hippocampal atrophy (de Leon et al., 1997a). The MCI participants in our sample had significantly reduced performance on the delayed paired associate test and on the digit span backwards test, but not in the paragraph recall test. The lack of difference between MCI and NE on the paragraph recall test is in contrast to previous observations from our

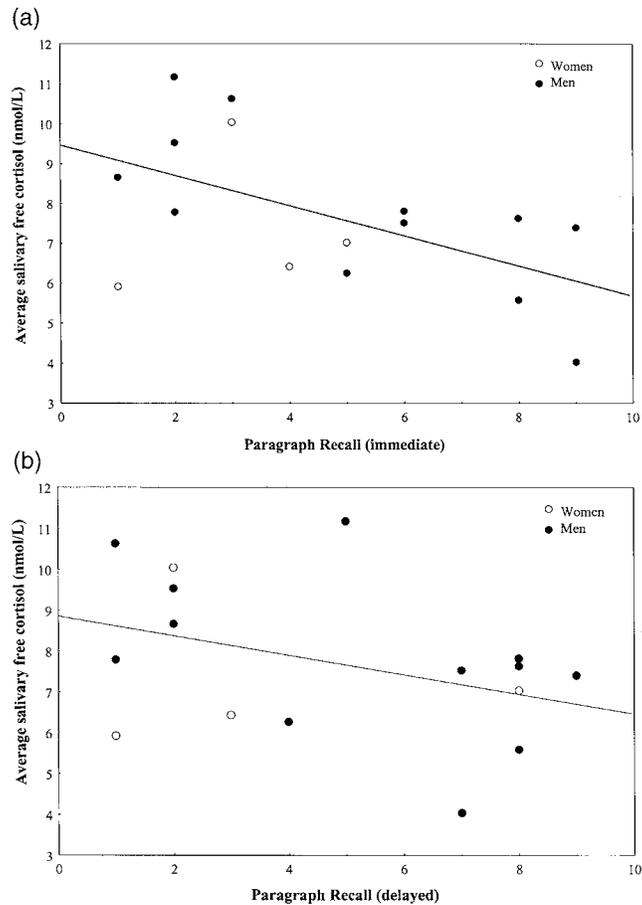


Fig. 2. (a) Association between average salivary cortisol levels and immediate recall performance in the paragraph recall test in subjects with MCI ( $n=16$ ,  $r=-0.55$ ,  $p<0.05$ ). (b) Association between average salivary cortisol levels and delayed recall performance in the paragraph recall test in subjects with MCI ( $n=16$ ,  $r=-0.38$ ,  $p=0.16$ )

laboratory (e.g. Convit et al. 1997, 2000; de Leon et al., 1997a). The results from the digit span test suggest that in addition to the hippocampus, involvement of other brain regions such as the prefrontal cortex (Moscovitch and Winocur, 1995; West, 1996) is possible among some of the MCI study participants. Future studies should measure cortisol levels as well as hippocampal and frontal lobe volumes in MCI subjects. Recent observations of high levels of glucocorticoid receptors in the primate prefrontal cortex (Patel et al., 2000; Sanchez et al., 2000) and that in rodents the prefrontal cortex is involved in HPA regulation (Diorio et al., 1993), emphasize the need for a combined assessment of prefrontal and medial temporal structures when investigating the interaction between cortisol levels, brain measures, and cognition.

As a group, elderly subjects had lower 9 a.m. levels than the young normal group,

with differences becoming significant in post hoc testing in the young normal versus MCI comparison. This could reflect the fact that the elderly subjects had an earlier wake-up time than the YN, which put them ahead in their circadian cycle. It is known that salivary cortisol levels increase after awakening before they start their continuous circadian decline (Van Cauter et al., 1996; Pruessner et al., 1997). In the current sample time of awakening was not correlated with the 9 a.m. measure, however only 27 subjects provided wake up time information. Future studies should standardize the time of awakening in order to avoid these problems with data interpretation.

Within the MCI group, higher average cortisol levels were associated with poorer performance in immediate paragraph recall. In addition, within the MCI group there was also a non-significant association between cortisol levels and performance on the delayed paragraph recall, where those individuals with higher salivary cortisol levels had lower scores. Since only one memory test significantly correlated with mean cortisol levels within the MCI group and multiple comparisons were made, this result has to be interpreted with caution. Moreover, cognitive testing and salivary sampling was not done on the same day. Nonetheless, these relationships between memory and salivary cortisol levels are in line with other observations in aging (O'Brien et al., 1994; Seeman et al., 1997; Lupien et al., 1998), AD (Oxenkrug et al., 1989; O'Brien et al., 1996), Cushing's disease (Starkman et al. 1992, 1999), depression (Rubinow et al., 1984), and Schizophrenia (Walder et al., 2000). Future studies should include more females with MCI since the association between cortisol levels and cognition might be stronger in older female participants (e.g. Oxenkrug et al., 1989; Seeman et al., 1997).

Performance on immediate recall of paragraphs might in part reflect attention or working memory, a function influenced by the integrity of prefrontal areas rather than by the hippocampus. In contrast delayed recall performance in this task is usually thought to depend on hippocampal integrity (see Squire, 1992) and this notion is supported by previous *in vivo* neuroimaging studies from our laboratory (Golomb et al. 1993, 1994; Convit et al., 1997). We found specific associations between delayed paragraph performance and hippocampus volume after accounting for the contribution of immediate paragraph performance (Convit et al., 1997). Given that among individuals with MCI there was a stronger correlation between mean cortisol levels and immediate recall, rather than delayed recall, this may indicate prefrontal cortex involvement in this group. This is consistent with previous reports (Lupien et al., 1999; Walder et al., 2000; Lyons et al., 2000; Wolf et al., 2001). Although our salivary cortisol day profiles were not higher among participants with MCI, whether cortisol levels are causally related to poorer memory in participants with MCI and/or can predict future cognitive decline remains to be established. Among normal elderly subjects, longitudinal changes in blood cortisol levels measured in the laboratory over 24 hours, are a better predictor of memory performance and hippocampal volumes than the cortisol levels measured in cross-section (Lupien et al., 1998). There are a few small studies demonstrating that among patients with mild to moderate AD cortisol levels were a predictor of future cognitive or clinical decline (Weiner et al. 1993, 1997; Umegaki et al., 2000). Peripheral cortisol levels

are among other potentially useful predictors, such as CSF cortisol and tau protein measurements (Hampel et al., 1999; Peskind et al., 2001), that need to be evaluated in future longitudinal studies with MCI participants.

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