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Correlation of high serum leptin levels with selected stress-associated salivary hormones in healthy young Arab men

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ABSTRACT

Background: Allostatic load is associated with the modern lifestyle of youth. The aim of this study is to evaluate the association between stress markers, such as salivary cortisol and dehydroepiandrosterone (DHEA) hormone levels, in Arab young men with high levels of leptin.

Methods: A total of 118 males aged 18–26 years were eligible to participate in a retrospective cross-sectional study. Participants were categorized into two groups: those with moderate serum leptin levels (<7 ng/ml) and those with high serum leptin levels (≥7 ng/ml). Serum leptin, salivary cortisol, and DHEA levels, as well as lipid profile and fasting blood glucose, were assayed for each participant.

Results: A significant decrease in the mean levels of morning salivary DHEA was observed in the high-leptin group compared to the moderate-leptin group ($p < 0.0001$). A significant increase was also observed in mean values of body weight and body mass index. A positive correlation was found between morning salivary DHEA and serum leptin levels in all subjects ($p = 0.003$). Pearson correlation analysis showed significant correlations between morning salivary DHEA, body weight, body mass index, and triglyceride levels.

Conclusion: The serum leptin level was proportional to the DHEA/cortisol imbalance, which was associated with allostatic load and the inability to manage stress in young males.

Introduction

Youth's modern lifestyle is accompanied by inadequate accommodation to chronic stress which is known as allostatic load. The allostatic load is characterized by impairment of glucocorticoid levels particularly cortisol hormone because of chronic stress, and loss of quality of life(1-4). Consequently, cortisol levels alteration has been linked to numerous stress-related conditions such as heavy cigarettes and waterpipe tobacco smoking, sleep deprivation, heavy coffee consumption and, hyperleptinemia (5-8). In relation to obesity, leptin is more reliable as an obesity marker than body mass index (9, 10). Although the remarkable response to stress with high cortisol in humans or corticosterone in animals has augmented the risk for diet-induced obesity, clinical trials of previous data were inconsistent (11-13). Several observational studies, as well as clinical trials, showed that there was a positive, or an inverse correlation between serum levels of cortisol and leptin (9, 12, 14, and 15). Dehydroepiandrosterone (DHEA) is one of the most important anti-ageing and youth stress predictors (16). It significantly reduces circulating levels and antagonizes the neurotoxic effects of cortisol(17,18). Furthermore, it has shown an inverse relationship to cortisol levels in response to CRH infusion(19). Nevertheless, a stress-buffering effect of DHEA or a reciprocal relationship between DHEA and cortisol is not yet approved(20). Further, an increased risk of allostatic load linked to a higher cortisol-DHEA ratio is still controversial (21, 22). In relation to obesity as a lifestyle stressor (23), the correlation is also unclear. It seems that the imbalance of the cortisol-DHEA ratio might be driven by adiposity, rather than the effect of age as an independent factor. In this context, the adiposity marker, leptin level, may be involved in the variation of the cortisol-DHEA ratio. Therefore, the current study aims to assess the correlation of high serum leptin levels with morning and midnight concentrations of salivary cortisol and DHEA ratio in healthy young men.

Methods

Study design and Participants

This retrospective cross-sectional study was carried out at the Applied Science Private University (ASU), Amman / Jordan, during the period from October 2018 to February 2019.

Young Arab male undergraduate and graduate students from ASU (from Jordan, Palestine, Iraq, Syria, Lebanon, Egypt, Algeria, Morocco, and Libya) aged from 18 to 26 years participated in the study. Participants filled out a questionnaire that includes lifestyle and anthropometric measures via an individual face-to-face interview with participants on the day of collecting blood samples. The total number of participants who were approached to participate in the study was 122, among which 7 students were excluded because they didn't meet the required criteria (4) or insufficient quantity of saliva (n=3). The participant who intermittently used any medication during the period of two months before the beginning of the study was excluded. Serum and salivary samples were analyzed for 115 participants as shown in Figure 1.

Participant categorization was based on data collected from several studies have been conducted on Arab young men from different countries with similar age groups and measured serum leptin levels (24-26). Based on a previous study (24) with some modification linked to , participants' leptin levels as well as BMI values, students were distributed into two groups: moderate levels of serum leptin (<7 ng/ml; ML) and high levels of serum leptin (≥7 ng/ml; HL). The anthropometric data, which included body weight (BW), height (Ht), and body mass index (BMI), were collected following standard procedures(27). Salivary and serum contents hormones and lipid profiles, as well as fasting blood glucose (FBG) were collected and measured at the laboratories of the department of clinical pharmacy and therapeutics at the ASU-Pharmacy College.

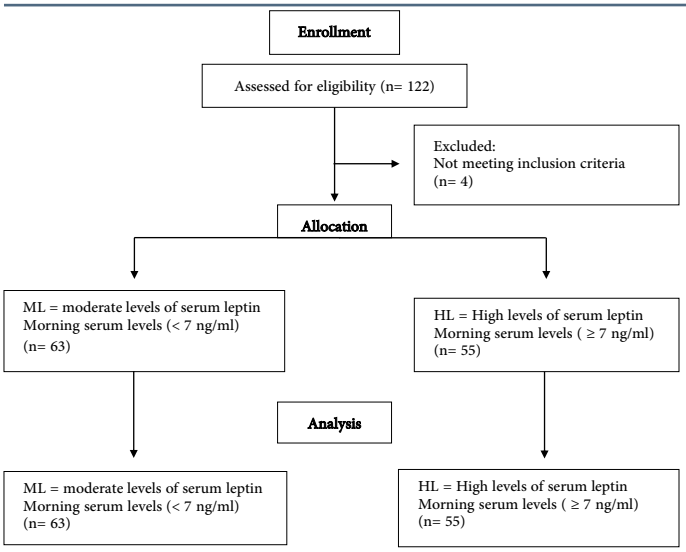


Figure 1. Schematic Diagram of Study Design.

The number of recruited participants was like a published cross-sectional study involving male university students (28).

Clinical parameters assays

The participants were supplied with a Salivette sampling device (made of cotton) and they also received verbal and written instructions that describe how to utilize it. It is known that; the highest cortisol levels are in the early morning wheats its lowest levels at midnight (29). Accordingly, midnight (between 11 and 12 a.m.) salivary cortisol (NS-C) and dehydroepiandrosterone (NS-DHEA) were collected in a Salivette by the students themselves according to the provided instruction from the research team. Morning salivary cortisol (MS-C) and dehydroepiandrosterone (MS-DHEA) were collected in a Salivette from the participants (8 and 9 a.m.) by the students themselves under the supervision of research assistants. The participants were also notified to passively drool through a straw into a tube, which was kept on ice to precipitate mucins, and then the samples were centrifuged (10,000 × g, 15 min, at 4°C). The supernatant (1 mL) was collected and stored at -80°C until assayed 2 weeks later. Salivary hormones (cortisol and DHEA) were assayed using an enzyme-linked immunosorbent assay (ELISA) kits, DRG International, Inc., USA). Polypropylene vials were used to store the fasting serum-leptin samples at -80°C after being liquidated prior to analysis 2 weeks later. Then, commercial leptin-enzyme immunoassay (EIA) kits were used to determine the serum leptin (DRG Diagnostics, Marburg, Germany) with an analytical sensitivity of 1.0 ng/mL, based on the specification of the manufacturer. One Touch meter (LifeScan, CA, USA) was used to measure fasting blood glucose (FBG). Serum lipid profile parameters: total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) using enzymatic colorimetric assay were also measured.

Statistical Analysis

The statistical software package, (SPSS Statistics version 21, Chicago, IL, USA) was used to analyze the data. The data collected were analyzed using the *t*-test statistical analysis to compare the mean differences between the clinical findings of both groups. On the other hand, the Pearson analysis was used to study any correlation between the serum-leptin levels and participants' characteristics. To evaluate the effects of independent variables (IDVs), the stepwise multiple regression analysis was used.

Results

Descriptive Characteristics:

The clinical and anthropometric characteristics are listed in Table 1. This table shows an independent *t*-test comparing the mean (± Standard Deviation) between study groups of the anthropometric and clinical characteristics participants. Significant differences in the means of serum leptin were observed between the two study groups ($p < 0.001$). Independent *t-tests* also showed significant differences in the means of MS-DHEA. Mean MS-DHEA was significantly lower in HL group than ML group (1.26 ± 0.5 vs1.7 ± 0.51 ng/mL, $p < 0.001$). Except for HDL-C, the means of all lipid profile parameters were higher in HL.

Table 1. Independent *t*-test comparing (Mean ± Standard Deviation) between study groups.

Variable	ML Mean ± SD, n=61	HL Mean ± SD, n=54	*p*-Value
Age (Year)	22.2 ± 1.83	22.3 ± 1.7	0.756
Serum Leptin	3.98 ± 1.88	19.05 ± 8.35	< 0.001
MS-DHEA (ng/mL)	1.7 ± 0.51	1.26 ± 0.5	< 0.001
NS-DHEA (ng/mL)	1.03 ± 0.46	1.1 ± 0.5	0.186
MS-C (ng/mL)	7.7 ± 3.2	8.2 ± 2.3	0.393
NS-C (ng/mL)	4.9 ± 2.2	5.7 ± 1.8	0.95
BW (kg)	71.0 ± 3.6	89.9 ± 11.1	< 0.001
Ht (cm)	176.1 ± 4.3	175.9 ± 5.3	0.61
BMI (kg/m²)	22.9 ± 2.2	29.21 ± 2.2	< 0.001
TG (mg/dL)	116.1 ± 44.8	158.4 ± 50.8	< 0.001
TC (mg/dL)	168 ± 27.1	184 ± 26.4	< 0.005
HDL-C (mg/dL)	51 ± 7.6	49.7 ± 7.3	0.154
LDL-C (mg/dL)	97.1 ± 27.4	116 ± 24.1	< 0.001
FBG (mg/dL)	86.1 ± 7.3	86.7 ± 9.8	0.66

ML: moderate leptin levels (<7 ng/ml), HL: high leptin levels (≥7 ng/ml), SD: standard deviation, MS-DHEA: morning salivary dehydroepiandrosterone, NS-DHEA: midnight salivary dehydroepiandrosterone, MS-C: morning salivary cortisol, NS-C: midnight salivary cortisol, BW: body weight, Ht: height, BMI: body mass index, TG: triglycerides, TC: total Cholesterol, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, FBG: fasting blood glucose.

Correlations of serum leptin levels with subjects' variables

Table 2 shows a significant negative correlation between M-DHEA and serum leptin (R=-0.251, $p < 0.01$) in the whole study sample (n=115). Except for HDL-C, Leptin levels showed a significant positive correlation with all lipid profile parameters. A strong significant positive correlation between leptin and BW was observed in this study (R=0.752).

Table 2. The Pearson correlations between subjects' characteristics and leptin serum level in all study samples (n=115).

Predictor	Unit	R
Age	Year	0.069
MS-C	ng/mL	0.116
NS-C	ng/mL	0.090
MS-DHEA	ng/mL	-0.251*
NS-DHEA	ng/mL	-0.141
BW	Kg	0.752*
Ht	cm	0.040
BMI	kg/m²	0.748*
TG	mg/dL	0.37*
TC	mg/dL	0.301*
HDL-C	mg/dL	-0.051
LDL-C	mg/dL	0.320*
FBG	mg/dL	0.037

R: Pearson linear correlation coefficient, MS-C: morning salivary cortisol, NS-C: midnight salivary cortisol, MS-DHEA: morning salivary dehydroepiandrosterone, NS-DHEA: midnight salivary dehydroepiandrosterone, BW: body weight (kg), Ht: height (cm), BMI: body mass index (kg/m²), TG: triglycerides (mg/dL), TC: total Cholesterol (mg/dL), HDL-C: high-density lipoprotein cholesterol (mg/dL), LDL-C: low-density lipoprotein cholesterol (mg/dL), FBG: fasting blood glucose (mg/dL).
* Correlation (2-tailed) is significant at the 0.01 level (*p*-value <0.01).

Correlations of morning salivary DHEA (MS-DHEA) with subjects' variables

Concerning the MS-DHEA correlations, a notable negative correlation (*p*-value <0.01) between MS-DHEA and some obesity parameters was observed. MS-DHEA showed a

correlation with TG, BMI, and BW (R= -0.292, -0.282, and 0.257), respectively as presented in Table. 3.

The multivariate association showed an influential relationship between the MS-C and TG levels on serum leptin levels in HL and ML (R=0.036 and $p<0.0001$). The stepwise multiple linear regression models were conducted to identify the multivariate associations that mediated lower MS-DHEA levels, which were observed in the HL group compared to the ML group. The MS-DHED levels in people with high levels of leptin (HL group) were significantly influenced by SM-C

Table 3. Pearson significant correlations of MS-DHEA with subjects' variables (n=115).

Variable	R
TG	-0.292*
BMI	-0.282*
BW	-0.257*

R: Pearson linear correlation coefficient, TG: triglycerides, BMI: n-body mass index, BW: body weight.
* Correlation (2-tailed) is significant at the 0.01 level (*p*-value <0.01).

levels (R=0.666, R^2=0.44, p<0.0001). The MS-C clarified approximately 44 % of the variance in MS-DHEA levels in young men with high serum levels of leptin (Table 4). On the other hand, the TG levels influenced MS-DHEA levels (R= 0.269, R^2= 0.072, *F*-test: 5.603, p<0.036), which explained approximately only 7 % of the variance in MS-DHEA levels among participants in the ML group.

Table 4. The multivariate association between the study variables and MS-DHEA in ML and HL study groups using stepwise regression.

Dependent Variable	Study Group	Univariate Effect Estimate	Coefficient				
			B	F	R	R^2	*p*-value
MS-DHEA	ML	TG	-0.003	5.603	0.269	0.072	0.036
	HL	MS-C	0.094	35.927	0.666	0.444	<.0001

ML: moderate leptin levels (<7 ng/ml), HL: high leptin levels (≥7 ng/ml), MS-DHEA: morning salivary dehydroepiandrosterone, TG: triglycerides, MS-C: morning salivary cortisol, *R*: Pearson linear correlation coefficient; R^2: determinant coefficient.

Discussion

This study was designed to assess the association of high serum leptin as an adiposity marker with alterations of salivary levels of cortisol hormone as a stress response, and DHEA as an anti-stress predictor in a representative sample of young Arab males. Furthermore, it was observed that the SM-DHEA was negatively associated with high serum leptin (HL) levels. Except for MS-DHEA, a slight elevation in the mean levels of MS-C was observed in the HL study group. These changes were accompanied by higher BMI values which can be attributed to students' allostatic load. While the antagonistic relationship between cortisol and DHEA, as part of the long-term consequences of stress, has been revealed in prior reports(30, 31). The DHEA antagonizes the neurotoxic effects of glucocorticoids on the memory center in the hippocampus(17, 18). The DHEA administration, in randomized clinical trials (RCTs), has been associated with reduced circulating levels of cortisol(17, 19). This association between the two salivary steroids was more obvious in young men than in older people(32). Therefore, DHEA has been ascribed as a potential stress-buffering hormone in youth. In the same context, DHEA levels proportionally have shown an ongoing decline with the individual's age(33). Consistently with our results, Japanese adult male workers over 50 years with higher cortisol - DHEAs ratio have shown an increased risk of sickness absence (21). This was consistent with other findings that suggested a higher ratio of DHEA to cortisol, might be associated with the term of improving an individual's health -related quality of life during ageing in Tai Chi practitioners(22). Nevertheless, DHEA-cortisol imbalance might be mediated by obesity status rather than an individual's age only. In this context, it has been mentioned that DHEA can improve glucose tolerance by converting excess body fat to lean muscle mass(20). The DHEA-cortisol imbalance has also been linked to obesity in metabolic syndrome conditions(13). However, regardless of serum leptin levels, the higher mean value of other obesity predictors such as TG and BMI seen in the HL study group compared to the ML may be additional evidence.

Conclusions

The findings of the current study observed that serum leptin levels are proportional to the MS-DHEA/cortisol decline that might be linked to allostatic load and loss of quality of life in youth. Therefore, the morning DHEA-cortisol ratio could be a new indicator of allostatic load and the inability to accommodate stress in overweighed and obese male youth.

Ethics approval and consent

Recruited participants were provided with informed consent, which contained details of the study protocol. The study was conducted in accordance with the Helsinki Declaration and Ethics approval was obtained from the Institutional Review Board (IRB) at the Applied Science Private University (Ethical approval No. 2018-PHA-2).

Data availability statement

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

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Declaration of Interest statement

The authors report no conflicts of interest in this work.

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