

Cardiac autonomic dysfunction in young obese males is not associated with disturbances in pituitary-thyroid axis hormones

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Abstract. – OBJECTIVE: Obesity has been associated with hypothyroidism and cardiac autonomic dysfunction. The present study aimed to investigate whether cardiac autonomic dysfunction in young obese males might be related to an underlying thyroid disturbance.

PATIENTS AND METHODS: On the basis of body mass index (BMI), 40 participants were grouped into normal weight group (NW; BMI = 18.5-25 kg/m²; n = 15), over weight group (OW; BMI = 25-29.9 kg/m²; n = 12) and obese group (OB; BMI ≥ 30 kg/m²; n = 13). Electrocardiogram was recorded using PowerLab system and the time and frequency domain measures of heart rate variability (HRV) were calculated. Fasting blood samples were drawn for measurement of serum thyroid stimulating hormone (TSH), total thyroxin (TT4) and total triiodothyronine (TT3) concentrations.

RESULTS: The levels of TSH, TT4 and TT3 were not significantly different between the groups. The frequency domain HRV parameter reflecting parasympathetic tone (high-frequency normalized units, HFnu) was significantly reduced in OB group. The parameters which reflect sympathetic activation (Heart rate, low-frequency normalized units; LFnu and the LF/HF ratio) were significantly increased in the OB group. HFnu was significantly and negatively correlated with BMI, waist hip ratio and body fat percentage, whereas LFnu and LF/HF ratio were significantly and positively correlated with the above mentioned parameters. No significant relationships were noted between the HRV parameters and the levels of TSH or thyroid hormones.

CONCLUSIONS: Cardiac autonomic dysfunction in obese young adult males is not linked with underlying thyroid disturbance.

Key Words:

Cardiac autonomic dysfunction, Obese males, Thyroid disturbance.

Introduction

Obesity is becoming a worldwide problem affecting all levels of socioeconomic sectors and is being described as a global epidemic^{1,2}. Over the years, obesity in adults has been found to be strongly related to increased morbidity and mortality in cardiovascular diseases^{3,4}. Though the pathophysiologic mechanisms of cardiovascular dysfunction in obesity has not yet been fully elucidated, altered of cardiovascular autonomic regulation has been proposed as a possible mechanism that link overweight and obesity with the increased prevalence of cardiovascular disease⁵.

Heart rate variability (HRV), a measure of the continuous variations in heart rate, is a sensitive and non-invasive method that represents beat-to-beat control mechanisms mainly by the autonomic nerve supply to the sinoatrial (SA) node^{6,7}. Increased HRV has been recognized as a factor that indicates a healthy heart with quickly response of autonomic nervous system and SA node to internal or external environmental changes^{7,8}. In contrast, a reduced HRV measures could reflect an altered sympathovagal balance of the SA node. This altered balance is characterised by a sympathetic activation and by a reduced vagal tone which has been strongly related to the pathophys-

iology of several diseases, including cardiovascular system diseases^{8,9}. The risk for altered cardiac autonomic function is significant in overweight and obese subjects. Previous studies using HRV methods to measure cardiovascular autonomic function have indicated that obese individuals have a significant reduction in parasympathetic activity and a significant increase in sympathetic modulation of cardiac function, indicating a shift in the sympathovagal balance towards sympathetic predominance^{10,11}.

The association between thyroid hormone and cardiac function is well established, and thyroid dysfunction, even mild, can significantly affect the cardiovascular system¹². It has been shown that hyperthyroidism and hypothyroidism are both associated with sympathetic over activity and decreased vagal modulation of the heart rate^{13,14,15}. An elevated serum concentration of thyroid stimulating hormone (TSH), symptomatic of subclinical hypothyroidism, was commonly reported in human obesity¹⁶. Therefore, it is plausible to propose potential relationships between cardiovascular autonomic function and an underlying thyroid disturbance in young adult obese males. However, it's remained unknown whether cardiac autonomic dysfunction in young adult obese males might be related to an underlying thyroid disturbance or not. We, therefore, formulated the hypothesis that obese young adult males, as compared with normal-weight counterparts, will show cardiac autonomic dysfunction that is characterized by sympathetic dominance on the autonomic cardiovascular system, and that these differences would be associated with thyroid dysfunction.

Patients and Methods

Patients and Study Design

The research proposal was approved by the Ethical Committee of the institution and written informed consent was obtained from all the participants prior to commencement. A total of 40 young adult males aged between 19 and 22 years were recruited from the medical and health science faculties at the University of Hail/KSA for a complete one day trial. The exclusion criteria included the presence of acute or chronic diseases, any medications use, abnormal resting electrocardiogram (ECG) and smoking. Validated questionnaire addressing age, history of chronic diseases and personal habits was self-administered. After that, all

subjects were exposed to anthropometric measurements including body weight, body mass index (BMI), waist/hip ratio (WHR), body fat percentage (BFP) and visceral fat area, (VFA) using InBody Composition Analyzer 720 (Biospace, Seoul, Korea). According to the guidelines of the National Institute of Health¹⁷, the participants were grouped based on the BMI into normal weight group (NW; BMI = 18.5-25 kg/m²; n = 15), over weight group (OW; BMI = 25-29.9 kg/m²; n = 12) and obese group (OB; BMI ≥ 30; n = 13).

Blood Collection and Analysis

Venous blood samples (10 ml) were obtained between 09:00 and 11:00 am after overnight (> 12 hr) fasting. Blood samples were drawn from an antecubital vein into vacutainer tubes without anticoagulant in a sitting position. For serum collection, tubes were incubated in an upright position at room temperature for 15-30 min to allow clotting before centrifugation (10 minutes, 3000 rpm). Serum was immediately stored at -70°C until further analysis. Thyroid tests included TSH (normal rang 0.30-4.00 mIU/l), total thyroxin (TT4; normal rang 4.4-11.6 µg/dl) and total triiodothyronine (TT3; normal rang 0.69-2.02 ng/ml) were measured using commercial enzyme-linked immunosorbent assay kits (HUMAN Diagnostics, Wiesbaden, Germany).

Assessment of Blood Pressure and HRV

Blood pressure was measured using mercury sphygmomanometers. ECG was digitally recorded in a quiet room (ambient temperature 22°C) with subjects lying in a supine position for 5 minutes using a biological amplifier (Bio Amp Model MLA2540, ADInstruments, Bella Vista, Australia) connected to a data acquisition system (Powerlab Model ML856, ADInstruments, Bella Vista, Australia). Standard time and frequency domain measures of HRV were calculated using HRV module LabChart 7.1 software (ADInstruments, Bella Vista, Australia). Time domain measures included heart rate, standard deviation of normal to normal intervals (SDNN) and the root mean square of successive RR intervals difference (RMSSD). Analysis of the power spectra was performed on two frequency ranges, revealing a low-frequency (LF) component between 0.04 and 0.15 Hz and a high-frequency (HF) component between 0.15 and 0.40 Hz. The LF and HF measures were expressed in normalized units (LFnu and HFnu). The low frequency: high-frequency ratio (LF/HF), an estimate of

sympathovagal balances in which a high ratio indicates greater sympathetic activity and a low ratio indicates greater parasympathetic activity, was also computed.

Statistical Analysis

All variables were reported as mean ± standard error of mean (SEM). Data were analyzed using a one-way ANOVA followed by Duncan’s post hoc test. Pearson’s correlation coefficient was used to evaluate the correlations between the parameters of HRV and anthropometric measurements and between the measures of TSH, TT3 and TT4 and the parameters of HRV. All statistical analyses were performed with the SPSS statistical package version 15.0 (SPSS Inc., Chicago, IL, USA). An α level of 0.05 was used to denote statistical significance.

Results

Mean values of anthropometric characteristics and thyroid parameters in the NW, OW, and OB groups are presented in Table I. By experimental design, the groups were similar by age and significantly differed (*p* < 0.01) by weight, BMI, WHR, BFP and VFA. No differences were noted among groups for serum TSH, TT4 and TT3 concentrations (*p* > 0.05). As shown in Table II, no associations were observed (*p* > 0.05) between circulating TSH or thyroid hormone levels and BMI, WHR, BFP and VFA.

Table III shows the differences in HRV variables among the three groups. HF component, expressed in normalized units, was significantly

lower (*p* < 0.05) in the OB group when compared with the NW group. Conversely, the LF component was higher (*p* < 0.05) in the OB group compared with the NW group. Thus, the LF/HF ratio, which is thought to express the sympathetic vs. parasympathetic balance, was higher (*p* < 0.05) in the OB group compared with the NW group indicated the sympathetic predominance over parasympathetic in this group. Time domain HRV indices (i.e. SDNN and RMSSD) were only numerically lower in the OB group compared with the NW group but did not differ significantly (*p* > 0.05; Table III), whereas heart rate was significantly higher (*p* < 0.05; Table III) in the OB group compared with the NW group. Post hoc testing revealed no differences (*p* > 0.05; Table III) between NW and OW or between OW and OB groups for all HRV variables.

Table IV shows the correlation between parameters of HRV and anthropometric measurements, as well as between parameters of HRV and TSH and thyroid hormones. HFnu was significantly and negatively correlated with BMI, WHR and BFP, whereas LFnu and LF/HF ratio were significantly and positively correlated with the above mentioned parameters. No significant relationships were noted between any of the HRV variables and the thyroid hormones or TSH levels (*p* > 0.05; Table IV).

Discussion

The main goal of the present study was to identify the cardiac autonomic regulation in young adult males with varying levels of obesity

Table I. Mean values of Anthropometric characteristics, TSH and thyroid hormones levels in the normal-weight, overweight, and obese groups.

Variable ¹	Normal weight	Over-weight	Obese	<i>p</i> value
N	15	12	13	
Age (years)	20.2 ± 0.28	20.7 ± 0.22	20.6 ± 0.51	ns
Weight (kg)	58.7 ± 2.17	79.6 ± 2.40*	99.9 ± 4.17* [‡]	0.0001
BMI (Kg/m ²)	20.2 ± 0.61	27.5 ± 0.43*	35.0 ± 1.3* [‡]	0.0001
BFP (%)	18.2 ± 1.45	28.6 ± 1.34*	41.8 ± 1.63* [‡]	0.0001
WHR	0.82 ± 0.009	0.90 ± 0.004*	0.97 ± 0.009* [‡]	0.0001
VFA (cm ²)	52.19 ± 4.63	89.8 ± 5.46*	145 ± 13.6* [‡]	0.0001
TSH (mIU/l)	1.79 ± 0.17	2.1 ± 0.34	1.84 ± 0.22	ns
TT4 (µg/dl)	7.35 ± 0.26	7.96 ± 0.33	7.35 ± 0.27	ns
TT3 (ng/ml)	1.27 ± 0.06	1.44 ± 0.11	1.47 ± 0.06	ns

Data are expressed as means ± SEM. ¹BMI: body mass index; WHR: waist/hip ratio; BFP: body fat percentage; VFA: visceral fat area; TSH: thyroid stimulating hormone; TT4: total thyroxin; TT3: total triiodothyronine; ns, non-significance. *Significantly different from normal-weight group, *p* < 0.01; [‡]Significantly different from over-weight group, *p* < 0.01.

Table II. Correlation between anthropometric measurements and thyroid parameters.

Variable ¹	BMI	BFP	WHR	VFA
TSH	0.051	0.096	0.048	0.012
TT4	0.015	0.136	-0.029	-0.070
TT3	0.244	0.244	0.158	0.147

¹BMI: body mass index; WHR: waist/hip ratio; BFP: body fat percentage; VFA: visceral fat area; TSH: thyroid stimulating hormone; TT4: total thyroxine; TT3: total triiodothyronine.

and to examine relationships between cardiac autonomic function and the thyroid status. Our main findings were: (1) an increase in body weight was accompanied with increase in heart rate and low HRV in OB but not OW young males, indicating an increased sympathetic and a reduced vagal modulation of sinus node; and (2) no evidences were found for an association between thyroid parameters within the normal range and the obesity indices, as well as between thyroid parameters and the cardiac autonomic dysfunction which observed in obese young adult males.

Power spectrum analysis of HRV can estimate the state of sympathovagal balance modulating SA node activity¹⁸. In addition to the RR interval, the normalized powers of the LF and HF components (LFnu and HFnu) of the HRV appear to be the most sensitive markers on an individual basis for sympathetic and vagal modulations, respectively¹⁸. As well, higher values of LF/HF ratio indicate a more sympathetically driven cardiovascular system^{6,7}. In the current study it was shown that the LF/HF ra-

tio, in addition to the LFnu component, was higher in the OB group compared with the NW group, indicating a shift in the sympathovagal balance toward an increment in sympathetic activation. Further, results of the present study show a lower parasympathetic activity in OB group compared with the NW group, as reflected by a significantly lower HFnu component. Obviously, sympathetic activation and diminished parasympathetic nervous system activity results in heart rate acceleration in the OB group (Table III). These results are in keeping with the results of previous investigators who found that obesity is related to sympathovagal imbalance characterized by depressed parasympathetic tone and increased sympathetic activity^{5,10,11,19,20}.

Interestingly, no differences were observed in HRV indices between the NW (BMI = 18.5-25 kg/m²) and OW (BMI = 25-29.9 kg/m²) groups (Table III). This finding expresses the fact that progression from overweight to obesity in young adult males is associated with changes in autonomic regulation of the cardiovascular system which are not fully recognized until the obesity is significantly increased. Our finding is in agreement with that of Kaufman *et al*²⁰, who observed no differences in HRV measures between the NW and OW children. Researchers have reported significant improvement in autonomic cardiac modulation through a shift toward greater vagal tone with diet-induced weight loss and exercise therapy^{8,21}. Therefore, interventions to increase HRV in overweight subjects, such as exercise therapy or dieting, may enhance vagal tone and thereby decrease their susceptibility to cardiac autonomic dysfunction.

Table III. Mean values of heart rate, blood pressure and heart rate variability parameters in the normal-weight, overweight, and obese groups.

Variable ¹	Normal weight	Over-weight	Obese	<i>p</i> value
HR (bpm)	66.8 ± 2.0	66.2 ± 2.7	75.6 ± 2.9*	0.027
Blood pressure, systolic (mmHg)	116 ± 1.52	120.2 ± 3.30	124.5 ± 2.71	ns
Blood pressure, diastolic (mmHg)	76.9 ± 1.25	79.8 ± 2.42	79.1 ± 1.91	ns
SDNN (ms)	67.6 ± 5.8	66 ± 6.8	62.7 ± 5.4	ns
RMSSD (ms)	72.1 ± 8.4	69.1 ± 13.4	60.5 ± 8.2	ns
LFnu	37.1 ± 3.4	46.5 ± 4.2	53.1 ± 4.4*	0.022
HFnu	52.1 ± 3.8	47.6 ± 4.3	36.1 ± 4.2*	0.024
LF/HF	0.85 ± 0.14	1.23 ± 0.28	2.02 ± 0.47*	0.034

Data are expressed as means ± SEM. ¹HR: heart rate; SDNN: standard deviation of normal to normal intervals; RMSSD: root mean square of successive RR intervals difference; HFnu: high-frequency normalized units; LFnu: low-frequency normalized units; LF/HF: low frequency/high-frequency ratio; ns: non-significance. *Significantly different from normal-weight group, *p* < 0.05.

Table IV. Correlation between parameters of heart rate variability, anthropometric measurements and thyroid parameters.

Variable ¹	BMI	BFP	WHR	VFA	TSH	TT4	TT3
HR (bpm)	0.381*	0.311	0.340*	0.284	0.193	0.049	0.048
SDNN	-0.166	-0.125	-0.029	-0.05	-0.063	-0.323 [#]	-0.046
RMSSD	-0.261	-0.261	-0.173	-0.183	-0.05	-0.226	-0.166
LFnu	0.434**	0.406**	0.385*	0.309 [#]	-0.039	0.041	-0.085
HFnu	-0.404**	-0.361*	-0.358*	-0.294 [#]	0.006	0.084	0.174
LF/HF	0.457**	0.427**	0.407**	0.352*	0.026	0.068	0.185

¹HR: heart rate; SDNN: standard deviation of normal to normal intervals; RMSSD: root mean square of successive RR intervals difference; HFnu: high-frequency normalized units; LFnu: low-frequency normalized units; LF/HF: low frequency: high-frequency ratio; BMI: body mass index; WHR: waist/hip ratio; BFP: body fat percentage; VFA: visceral fat area; TSH: thyroid stimulating hormone; TT4: total thyroxine and TT3: total triiodothyronine. [#]*p* < 0.10; **p* < 0.05; ***p* < 0.001.

Several authors have observed normal, reduced or elevated thyroid hormones and TSH baseline concentrations in adult obese individuals²². The mean serum levels of TSH, as well as the levels of thyroid hormones (TT3 and TT4) were not significantly different between the groups in this study. In addition, no associations were observed between circulating TSH and thyroid hormone levels and the body compositions. Our findings are in agreement with Manji et al²³, who found no difference in serum TSH between euthyroid obese subjects and the control group. Our findings are also consistent with the previous observations of Roef et al²⁴, who described no associations between TSH and body composition among euthyroid young men. However, in contrast, other authors found that in euthyroid adults without a history of thyroid disease, BMI was positively correlated to serum TSH, negatively to serum free T4 and had no correlation to serum free T3²⁵. In our study, all subjects were actually in a euthyroid state as the concentrations of TSH, TT3 and TT4 were within the normal range in all groups. This might be a potential elucidation for the lack of associations between TSH and the parameters of body compositions in this study as the associations with TSH in other studies can be caused by subclinical thyroid dysfunction²⁴. Additionally, the lack of associations between thyroid hormones and weight or fat mass in our subjects can be explained by that peripheral tissue metabolism of thyroid hormones was not affected by body fat mass²⁶.

Similarly with our observations for body composition, all the measured HRV variables were not correlated with the TSH, TT3 and TT4 levels. Therefore, it is evident from the present study that alteration in the cardiovascular autonomic function in young obese adult males was

not linked to the levels of thyroid hormones and TSH. According to our knowledge, no any previously published paper pertaining to the association between thyroid status and HRV parameters in a population of healthy euthyroid young men. However, hypothyroidism and hyperthyroidism have been associated with sympathetic over activity on the autonomic cardiovascular system^{13,14,15}. Though the findings of the present study do not illustrate a relationship between cardiac autonomic dysfunction and thyroid profile in obese subjects, the association of high body fat compositions (BMI, BFP and VFA) and a shift in cardiac sympatho-vagal balance towards a more sympathetic state implies that the degree of obesity determines cardiac sympathovagal balance in young adult healthy males. One can hypothesize that obesity might be associated with increases in many hormonal and metabolic parameters that may cause increased sympathetic activity and decreased parasympathetic activity. For example, serum leptin concentrations, an adipose tissue-derived hormone, are correlated with the BFP and have been shown to excite the sympathetic nervous system²⁷. Insulin resistance, elevated catecholamine levels and the degree of hyperlipidemia have also been proposed as potential mechanisms underlying the association between obesity and cardiac autonomic dysfunction²⁸⁻³⁰.

Conclusions

Our study demonstrates that young obese males have an abnormal cardiac autonomic function that could represent a risk for adverse cardiovascular events. The shift in cardiac sym-

pathovagal balance toward depressed parasympathetic tone and increased sympathetic activity are associated with the degree of obesity, while TSH and thyroid hormones appear to play no role on cardiac autonomic dysfunction in young obese males.

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Conflict of Interest

The Authors declare that there are no conflicts of interest.

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