# Cardiac changes with subclinical hypothyroidism in obese women

## Obez kadınlarda subklinik hipotiroidizmle birlikle kardiyak değişiklikler

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## ABSTRACT

***Objectives:*** Obesity has been linked to a spectrum of minor cardiovascular changes. The aim of this study was to determine the effect of obesity on cardiac functions and its relations with subclinical hypothyroidism in healthy women.

***Study design:*** Eighty-eight consecutive "healthy" females (mean age: 31.2±6.6 years) were included in the study. Thyroid function tests and echocardiography studies were performed in all patients. Height, weight, and waist and hip circumference were also measured. A body mass index (BMI) above 30 kg/m$^2$ was considered obese.

***Results:*** Left ventricular mass (LVM) was higher in obese subjects (p<0.001). Doppler-derived indices of LV diastolic filling showed clear abnormalities of myocardial relaxation in obese subjects with higher E/e' (p=0.001) and larger left atrial volume (LAV) (p<0.001). LV myocardial performance index was also significantly higher in obese subjects (p=0.033). Thyroid-stimulating hormone (TSH) levels were significantly higher in obese subjects (p=0.011) and were positively correlated with BMI, waist circumference, LAV, and LVM. The prevalence of abnormal systolic and diastolic functions showed stepwise increases with higher TSH levels in obese subjects. Multiple regression analysis was used to evaluate the association of E/e' with anthromorphometric and biochemical parameters, and waist circumference was found to be the strongest independent variable correlated with the E/e' ratio.

***Conclusion:*** Cardiac structural and functional deteriorations may be related with subclinical hypothyroidism in obese subjects.

## ÖZET

***Amaç:*** Obezitenin değişen yoğunlukta kardiyovasküler değişikliklere neden olduğu bilinmektedir. Bizim bu çalışmada amacımız sağlıklı kadınlarda obezitenin kalp fonksiyonları üzerine olan etkisini ve subklinik hipotiroidizmin olaya katkısını araştırmaktır.

***Çalışma planı:*** Çalışmaya ortalama yaşı 31.2±6.6 olan 88 sağlıklı kadın alındı. Tüm olgularda tiroit işlevleri değerlendirildi ve ekokardiyografik inceleme yapıldı, boy, kilo, bel ve kalça çevresi ölçüldü. Beden kütle indeksi (BKİ) >30 kg/m$^2$ olanlar obez olarak değerlendirildi.

***Bulgular:*** Sol ventrikül kitlesi (SVK) obez olgularda daha yüksek bulundu (p<0.001). Doppler ile gösterilen sol ventrikülün diyastolik doluş parametreleri obezlerde bozuk olarak saptandı. Obez olgularda E/e' oranı daha yüksek (p=0.001) ve sol atriyum hacmi (SAH) daha fazla saptandı (p<0.001). Sol ventrikül TEİ indeksi obezlerde daha yüksek bulundu (p=0.033). TSH düzeyi obez hastalarda anlamlı olarak yüksekti (p=0.011). TSH ile BKİ, bel çevresi, SAH, SVK ve sol ventrikülün miyokart performans indeksi arasında pozitif korelasyon saptandı. Obezlerde yüksek TSH değeri ile birlikte sistolik ve diyastolik fonksiyonlarda bozulma olduğu görüldü. Multipl regresyon analizi ile E/e' oranının antropometrik ve biyokimyasal parametreler ile olan ilişkisi değerlendirildi. Bel çevresi, E/e' oranı ile bağlantılı, güçlü, bağımsız değişken olarak saptandı.

***Sonuç:*** Sonuç olarak kalpte yapısal ve fonksiyonel bozulmaların obezlerde subklinik hipotiroidi ile ilişkili olabileceği düşünüldü.

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Obesity has become an epidemic condition and is associated with an increased risk of hypertension, diabetes, hyperlipidemia, sleep apnea, coronary heart disease, and stroke.[1,2] Several clinical studies have evaluated the issue of hormonal changes associated with obesity[3,4] and consistently reported changes in thyroid function parameters in obese subjects.[5,6] Obesity has been linked to a spectrum of cardiovascular changes.[7,8] It is important to detect these changes early, as it is possible to reverse them with treatment in the early stages of the disease.

The aim of this study was to determine the effect of obesity on cardiac functions and its relations with subclinical hypothyroidism in healthy females.

## PATIENTS AND METHODS

Eighty-eight consecutive healthy females (mean age: 31.2±6.6 years) who had admitted to our cardiology outpatient clinic were recruited to the study. The medical records of all subjects were assessed. Subjects with a history of established heart disease, type II diabetes mellitus, hypertension, dyslipidemias, thyroid diseases, and active inflammation were excluded from the study. Prediabetic subjects with fasting glucose >100 mg/dl were also excluded according to the American Diabetes Association (ADA) criteria.[9] Height, weight and waist circumference were also measured. All subjects underwent biochemical laboratory evaluation for blood tests and transthoracic echocardiography for standard echocardiographic examination. According to their body mass index (BMI), the subjects were divided into two groups as BMI <30 kg/m² (group 1) and BMI ≥30 kg/m² (group 2). We considered obesity as BMI ≥30 kg/m² as expected in the following literature.[10]

The investigation was conducted in accordance with the guidelines proposed in the Declaration of Helsinki. The study protocol was approved by the local ethics committee and informed consent was obtained from all participants. No funding was received to support this work.

### Anthromorphometry and laboratory tests

Body mass index was calculated as weight (in kilograms) divided by the square of height (in meters). Waist circumference (in centimeters) was measured from the midpoint between the lowest rib and the iliac crest, with the subject standing.

**Abbreviations:**

| | |
|---|---|
| *BMI* | *Body mass index* |
| *FT* | *Free triiodothyronine* |
| *HDL* | *High-density lipoprotein* |
| *LAV* | *Left atrial volume* |
| *LDL* | *Low-density lipoprotein* |
| *LVEF* | *Left ventricular ejection fraction* |
| *LVM* | *Left ventricular mass* |
| *MPI* | *Myocardial performance index* |
| *TDI* | *Tissue Doppler imaging* |
| *TSH* | *Thyroid-stimulating hormone* |

Blood samples were obtained after at least 12 hours of fasting. Fasting glucose levels were assessed by routine laboratory techniques. Serum thyroid hormone levels were measured by ultrasensitive immune radiometric assay using auto-analyzer systems, according to the manufacturer's instructions. The normal values were as follows: thyroid-stimulating hormone (TSH): 0.27-4.2 ng/ml, free triiodothyronine (FT3): 1.6-4.7 pg/ml, and free thyroxine hormone (FT4): 0.61-1.12 ng/ml.

### Echocardiography

Echocardiographic examinations were performed according to the American Society of Echocardiography recommendations[11] with a Vivid 3 instrument (General Electric, Horten, Norway) and a 2.5 MHz transducer. All echo-Doppler studies were carried out by the same observer who was unaware of the clinical data in order to avoid inter-reader variability. Measurements were made on three consecutive beats and the results were averaged. Images were recorded digitally to an online system for measurement and analysis. Standard echocardiographic analysis included two dimensional, M-mode, and Doppler flow measurements.

Left ventricular ejection fraction (LVEF) was measured with modified Simpson's method from two-dimensional echocardiographic tracings obtained in apical four-chamber view, and other echocardiographic measurements were assessed according to the American Society of Echocardiography guidelines.[11] Left ventricular mass (LVM) was calculated using the equation described by Devereux.[12] The left atrial volume (LAV) was calculated using the area-length method. Using this method, the area of the left atrium was measured from both apical views by planimetry (A1 and A2). A linear dimension was measured from the center of the mitral annulus to the superior border of the chamber (L). The LAV was then calculated as [(0.85 × A1 × A2) / L].[13] Diastolic functions were evaluated by mitral inflow parameters (E, A, deceleration time [DT], E/A ratio).[14]

Tissue Doppler echocardiography [tissue Doppler imaging (TDI)] was performed from the apical four-chamber view by placing a 5-mm sample volume to the basal septum and lateral mitral annulus using pulsed-wave TDI as previously described.[11] Settings were adjusted for a frame rate between 120 and 180 Hz, and a cine loop of 3-5 consecutive heart beats were recorded. TDI-derived systolic, early and late diastolic indices were measured and averaged for global systolic and diastolic function.

Myocardial performance index (MPI) was calculated as the sum of isovolumic contraction time and isovolumic relaxation time divided by ejection time[15] (Fig. 1).

*E/e'ratio:* Early diastolic mitral inflow velocity (E) was measured using the pulsed- wave Doppler method by placing the sample volume at the level of the mitral valve leaflet tips. The tissue Doppler-derived early diastolic velocity (e') was measured from the average of septal and lateral tissue velocities in the apical four-chamber view.[11] The examinations were performed by the same operator for all participants in the study.

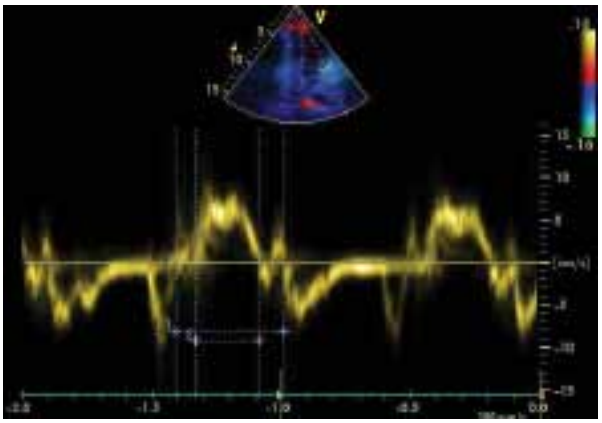

**Figure 1.** Tissue Doppler echocardiography images for calculation of myocardial performance index.

## Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) 11.0 for Windows. Data are presented as mean±SD, controlled for normal distribution by Kolmogorov-Smirnov test. Differences between any two groups were compared by Mann-Whitney U-test because of abnormal distribution. Categorical data between two or more groups were compared by the Pearson $\chi^2$ test. The correlation of continuous variables was analyzed by Pearson and categorical variables by Spearman correlation analysis. Logistics regression analysis was used to identify the independent predictors related with BMI from among hormonal and echocardiographic parameters. A probability value of $p<0.05$ was considered as significant.

## RESULTS

Eighty-eight consecutive females (mean age: 31.2±6.6 years) were included. All the patients were asymptomatic and in sinus rhythm. Findings of the physical examination, medical history, and electrocardiography were found normal. The clinical characteristics of the study population are shown in Table 1. Both heart rate and blood pressure were comparable between the two groups. TSH levels were significantly higher in obese subjects (p=0.05). FT3 and FT4 levels were in the normal ranges and did not differ between groups. Waist circumference was significantly higher in obese subjects (p<0.001). Table 1 summarizes Doppler-echocardiographic results. No clear evidence of systolic dysfunction was found between the two groups, but LVMs were higher in the obese subjects (p=0.002). Doppler-derived indices of LV diastolic filling showed clear abnormalities of myocardial relaxation, as indicated by higher E/e' (p=0.031), LAV (p<0.001) and left ventricle MPI (p=0.004) in the obese subjects (Fig. 2). We evaluated hypothyroidism in the obese subjects. Obese subjects were divided into two groups and compared according to mean TSH levels (Group a <2.2 mg/dl [n=28], group b ≥2.2

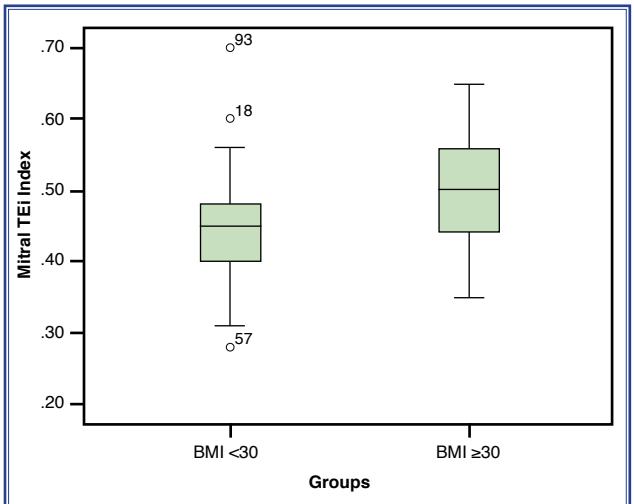


**Figure 2.** Correlations of myocardiyal performance index with body mss index (BMI).

**Table 1. Demographic and echocardiographic results**

| | Non-obese group (BMI <30) (n=44) | | Obese group (BMI ≥30) (n=44) | | *p* |
|---|---|---|---|---|---|
| | Mean±SD | Min-Max | Mean±SD | Min-Max | |
| Age (years) | 29.9±5.6 | 17-42 | 32.4±7.4 | 18-47 | 0.189 |
| Waist circumference (cm) | 90.4±8.3 | 68-107 | 106.9±9.1 | 92-140 | **<0.001** |
| TSH | 1.8±1.3 | 0.24-6.3 | 2.4±1.5 | 0.27-7.91 | **0.05** |
| FT4 | 1.1±0.7 | 0.7-2.1 | 1.0±0.6 | 0.6-2 | 0.245 |
| FT3 | 2.8±0.7 | 0.65-3.47 | 2.7±0.7 | 0.58-3.15 | 0.321 |
| Fasting glucose (mg) | 86.2±8.2 | 70-100 | 89.4±7.3 | 70-100 | 0.109 |
| Triglycerides (mg/dl) | 99.5±44.7 | 44-218 | 121.3±64.2 | 33-327 | 0.051 |
| T-Chol (mg/dl) | 186.2±35.7 | 110-286 | 187.8±33.9 | 121-271 | 0.83 |
| HDL (mg/dl) | 55.5±12.2 | 34-86 | 50.2±9.1 | 32-75 | **0.02** |
| LDL (mg/dl) | 113.8±23.5 | 64-171 | 120.6±27.9 | 62-181 | 0.21 |
| Systolic AP (mmHg) | 116.5±12.8 | 80-135 | 112.2±12.7 | 90-135 | **0.09** |
| Diastolic AP (mmHg) | 76.8±7.7 | 60-93 | 73.9±8.8 | 60-94 | **0.08** |
| LVEF (%) | 61.3±2.3 | 57-68 | 61.3±2.0 | 58-65 | 0.944 |
| LVM (g) | 132.5±34.3 | 54.9-232.7 | 155.1±31.5 | 98.7-221.6 | 0.002 |
| Mitral dec T (msn) | 184.8±31.7 | 121-254 | 197.5±36.3 | 114-267 | **0.1** |
| E/e' | 7.0±1.5 | 4.3-12.4 | 7.8±1.8 | 4.4-13.2 | 0.031 |
| Mitral Tei index | 0.44±0.07 | 0.28-0.7 | 0.49±0.08 | 0.35-0.65 | **0.004** |
| LAV ($mm^3$) | 41.8±9.6 | 18.4-63 | 53.8±13.1 | 34.1-81.6 | **<0.001** |

BMI: Body mass index; TSH: Thyroid-stimulating hormone; FT3: Free triiodothyronine; FT4: Free thyroxine hormone; T-Chol: Total cholesterol; HDL: High-density lipoprotein; LDL: Low-density lipoprotein, AP: Arterial pressure; LVEF: Left ventricular ejection fraction; LVM: Left ventricular mass; Mitral dec T: Mitral deceleration time; LAV: Left atrial volume.

[n=16]). The prevalence of abnormal systolic and diastolic functions showed stepwise increases from group a to group b, but the difference was not significant. LMI (82.7±11.3, 86.2±14.2; p=0.39), LAV index (28±4.6, 30.9±7.5; p=0.14), LVEF (61.5±2, 60.6±1.7; p=0.18), LV MPI (0.40±0.07, 0.51±0.09; p=0.39), and RV MPI (0.27±0.04, 0.28±0.12; p=0.74). Clinical hormonal and echocardiography parameters that correlate with BMI and TSH are demonstrated in Tables 2 and 3. Multiple regression analysis was used to evaluate the association of E/e' with anthromorphometric and biochemical parameters (TSH levels, fasting glucose, total cholesterol, triglyceride, high-density (HDL) and low-density (LDL) lipoprotein levels, BMI, waist circumferences, and systolic and diastolic arterial pressure). It was observed that E/e' was significantly associated only with waist circumferences (standardized β coefficient= 0.432, p=0.04) (Fig. 3). Other parameters were not significantly associated with E/e': TSH (standardized β coefficient= 0.146, p=0.14), fasting

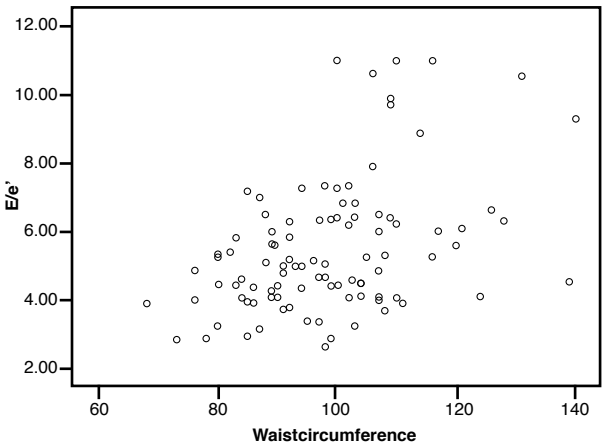


**Figure 3.** E/e' ratio was correlated significantly with waist circumference.

**Table 2. Correlations of BMI with other echocardiographic and anthromorphometric parameters**

| Body mass index | Pearson correlation | Significance (2-tailed) |
|---|---|---|
| Thyroid-stimulating hormone | 0.345 | **0.001** |
| Age (year) | 0.131 | 0.228 |
| Waist (cm) | 0.885 | **<0.001** |
| Left ventricular mass (g) | 0.574 | **<0.001** |
| Left ventricular ejection fraction (%) | -0.21 | 0.849 |
| Left ventricular TEI index | 0.279 | **0.009** |
| Mitral pressure HT (msn) | 0.195 | 0.079 |
| Left atrial volume (mm³) | 0.562 | **<0.001** |
| E/e' | 0.360 | **<0.001** |
| Mitral e' | -0.320 | **0.003** |

TEI: Total ejection isovolume; HT: Half-time; MIT e': Tissue Doppler E wave of mitral annulus.

**Table 3. Correlations of TSH with other echocardiographic and anthromorphometric parameters**

| TSH | Pearson correlation | Significance (2-tailed) |
|---|---|---|
| Body mass index (kg/m²) | 0.345 | **0.001** |
| Age (year) | 0.147 | 0.171 |
| Waist (cm) | 0.297 | **0.006** |
| Left ventricular mass (g) | 0.247 | 0.022 |
| Left ventricular ejection fraction (%) | 0.073 | 0.502 |
| Left ventricular TEI index | 0.254 | 0.018 |
| Mitral pressure HT (msn) | 0.195 | 0.087 |
| Left atrial volume (mm³) | 0.347 | **0.001** |
| E/e' | 0.360 | 0.136 |
| Mitral E TDI | -0.104 | 0.341 |

TEI: Total ejection isovolume; TSH: Thyroid-stimulating hormone; HT: Half-time; Mitral E TDI: Tissue Doppler E wave of mitral annulus.

glucose (standardized β coefficient= -0.101, p=0.34), total cholesterol (standardized β coefficient= 0.218, p=0.03), triglycerides levels (standardized β coefficient= 0.218, p=0.03), HDL levels (standardized β coefficient= -0.152, p=0.17), LDL levels (standardized β coefficient= 0.153, p=0.13), BMI (standardized β coefficient= -0.022, p=0.88), and systolic (standardized β coefficient= -0.088, p=0.61) and diastolic (standardized β coefficient= 0.055, p=0.74) arterial pressure.

## DISCUSSION

The results of our study demonstrated that cardiac structural and functional deteriorations were related with subclinical hypothyroidism in obese subjects.

In the obese patients, an increment in circulating plasma volume occurs, and consequently, blood volume rises, which leads to an important increase in the peripheral vascular bed. To compensate for the augmentation of the blood volume and the capillary net, the cardiac output is elevated. Increased stroke volume and cardiac output lead to dilatation of the heart chambers and eccentric LV hypertrophy.[13] Several studies have confirmed the increase in LV diameters, in addition to wall thickness and ventricular mass, especially in obese subjects.[16-18] In our study, LVM and LAV were increased with obesity. In some studies, LV systolic function was shown to be preserved in milder degrees of obesity,[19-21] while other studies have shown subclinical depression of LV function.[21]

In our study, we found no systolic dysfunction and LVEF was similar in the two groups.

Previous reports on diastolic function in obese subjects have reported variable results.[22,23] Earlier studies in obese individuals have reported inconsistent changes in LV filling indices.[20] Such disparities in simple flow measures may reflect the sensitivity of transmitral flow indices to loading conditions as well as the influence of increased LV mass.[23,24] The interpretation of transmitral flow in relation to tissue diastolic velocity may be a better means of assessing diastolic function especially given the intravascular volume expansion in obese subjects. The combination of E with peak e' velocity (i.e., E/e' ratio) is assumed to overcome the influence of ventricular relaxation on peak E velocity and reflect left atrial pressure.[11] In our study, we found an increased E/e' ratio in obese patients. E/e' was independently associated with waist circumferences (Fig. 3). The MPI is an echocardiographic parameter that correlates with invasive measurements and is used to evaluate both systolic and diastolic functions.[15] Some previous studies have shown higher MPI values in obese subjects.[25] Koç et al. found no change in MPI with obesity.[26] In our study, we found higher LV MPI values in obese subjects (Fig. 1).

In previous studies, serum TSH level in obese patients was higher when compared to healthy controls.[27,28] Unlike TSH, the circulating levels of free thyroid hormones vary, as increased or decreased serum concentrations of FT3,[27,28] with normal or decreased FT4/FT3 ratios.[27,28] In our study, we found the level of TSH obviously higher in the obese group than in the non-obese group. FT3 and FT4 were found similar between the two groups. We also found a significant correlation between TSH and waist circumference. A cause and effect relation between obesity and hypothyroidism remains controversial today. Verma et al. found that obesity was higher in overt hypothyroidism than in subclinical hypothyroidism, and more patients were overweight in the overt hypothyroidism group than in the subclinical hypothyroidism group.[29] In our study, we found a trend to obesity with increased TSH. In previous studies, it was shown that weight decreases following treatment for overt hypothyroidism.[30] However, there remains no clear knowledge about treatment in subclinical hypothyroidism.

Some earlier studies have suggested that subclinical hypothyroidism was associated with ventricular deterioration[31] and increased risk of coronary heart disease events.[27] Our study also demonstrated that TSH was correlated with LVM and LAV, which are the well-known echocardiographic indices of poor prognosis. In our study, LV MPI was increased and significantly correlated with higher TSH level. We found a prevalence of abnormal systolic and diastolic functions, which showed stepwise increases with subclinical hypothyroidism in obese subjects.

In conclusion, cardiac structural and functional deteriorations may be related with subclinical hypothyroidism in obese subjects. Treatment of subclinical hypothyroidism could facilitate weight reduction and could reverse cardiac dysfunction. Further prospective studies are needed to support this statement.

## Limitation

Obesity was measured using only BMI. Ultrasonography to determine abdominal obesity may also be used for better clinical results. Novel echocardiographic modalities for detection of ventricular systolic and diastolic dysfunction might influence our results. The selection of the study population, which included only healthy females, precludes extrapolation of our results to the general population.

***Conflict-of-interest issues regarding the authorship or article: None declared***

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*Key words:* Adult; body constitution; female; hypothyroidism; obesity / blood / physiopathology; thyroid function tests; thyroid gland.

*Anahtar sözcükler:* Erişkin; vücut yapısı; kadın; hipotiroidizm; obezite / kan / fizyopatoloji; tiroit işlev testi; tiroit bezi.