Body Fat Distribution and Cardiovascular Disease Risk Factors in Pre- and Postmenopausal Obese Women with Similar BMI

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Abstract. The aim of this study is to determine the body fat distribution and cardiovascular disease risk factors in pre- and postmenopausal obese women matched for weight, height and body mass index (BMI). Study group consisted of 405 premenopausal overweight/obese (BMI >27 kg/m², mean 37.83 ± 6.91 kg/m²) and 405 postmenopausal overweight/obese (BMI >27 kg/m²), BMI-matched (mean 37.77 ± 6.84 kg/m²) women. None of the women were on hormone replacement therapy. Insulin resistance was evaluated by “homeostasis model assessment” (HOMA) formula. Intraabdominal fat volume was calculated according to the following formula: IAF (L) = [(0.370 × abdominal sagittal diameter) – 4.85]. Age, waist circumference, waist to hip ratio (WHR) and intraabdominal fat volume were significantly higher in postmenopausals compared with BMI-matched premenopausal women (p<0.001). Systolic and diastolic blood pressure, glucose, uric acid, cholesterol and triglyceride were significantly higher (p<0.001) and HDL-cholesterol was significantly lower (p<0.05) in postmenopausals. No significant differences were observed with respect to insulin and HOMA. When age-matched pre- and postmenopausal women were compared, only total cholesterol was significantly higher in the postmenopausal group. However, older postmenopausal women (>50 years) had significantly higher systolic blood pressure, waist circumference, WHR, glucose and uric acid concentrations compared with younger (≤50 years) postmenopausals. It is concluded that an increase in abdominal fat accumulation and unfavorable alterations in risk factors disturb postmenopausal obese women even if total body weight and BMI do not change during menopause transition. Ageing, particularly throughout the postmenopausal years, has important effects on the detrimental changes associated with menopause.

Key words: Menopause, Abdominal obesity, Risk factors

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AN increase in the incidence of atherosclerotic cardiovascular disease is observed in women after menopause [1]. An increase in intraabdominal fat and a more atherogenic lipid profile may be operative for this observation [1, 2]. Previous studies indicated that the menopause transition is associated with unfavourable changes in body composition and abdominal fat deposition [1–6]. The consequences of these changes lead to augmentation of components

of the cluster of metabolic abnormalities associated with central obesity and insulin resistance.

Our aim is to determine body fat distribution and cardiovascular disease risk factors in pre- and postmenopausal obese women matched for weight, height and body mass index (BMI), in a retrospectively designed study.

Materials and Methods

BMI matched pre- and postmenopausal women were retrospectively selected from recorded data file of outpatient obesity clinic of Istanbul Medical Faculty between the years 1998–2001 according to

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the following criteria. A total of 1475 obese women were admitted to our obesity clinic between this period. The study group was composed of 405 premenopausal overweight and obese (BMI >27 kg/m², mean BMI 37.8 ± 6.9 kg/m²) and 405 postmenopausal overweight and obese (BMI >27 kg/m², mean BMI 37.7 ± 6.8 kg/m²) BMI-matched women. Selected premenopausal women have regular menstrual cycles and a follicle-stimulating hormone level less than 30 IU/L. All of the premenopausal women had weight stability during the 6 months prior to admission and a normal electrocardiogram at rest. None of the premenopausal women had a history or current diagnosis of diabetes, ischemic heart disease, hypertension (systolic and/or diastolic blood pressure $>160/95$ mmHg) or any other chronic diseases. None of them were taking oral contraceptives or medications that could affect body composition and metabolic functions.

Postmenopausal women were identified by the absence of menses for at least 12 months and a follicle-stimulating hormone level >30 IU/L. The exclusion and inclusion criteria for postmenopausal women were the same as premenopausal women. None of the postmenopausal women were on hormone replacement therapy. Additional exclusion criteria for postmenopausal women included a history of premature menopause (before 40 years old).

Obese women attended the outpatient obesity clinic after an overnight fast of 10–12 hour. A standardized clinical, anthropometric and laboratory evaluation was performed on all subjects according to our patient assessment protocol of outpatient obesity clinic. This included assessment of daily eating and physical activity patterns, smoking and alcoholic drinking habits, pharmacological drug use, family history, electrocardiogram, biochemical (glucose, uric acid, total and HDL cholesterol, triglyceride concentrations) and hormonal (basal insulin, thyroid and gonadal hormones) determinations and overnight dexamethasone suppression test where necessary. A general physical examination involved the measurement of height (to the nearest cm, without shoes), weight (to the nearest 0.1 kg, without coats), waist circumference (as the minimum value between iliac crest and the lateral costal margin) and hip circumference (as the maximum value over the buttocks). Body mass index (BMI) was calculated as the ratio of weight (kg) divided by height (m)

squared. Waist to hip ratio (WHR) was calculated as waist circumference (cm) divided by hip circumference (cm). Abdominal sagittal diameter was defined as the maximum diameter of the abdomen in the sagittal plane and was measured by body perimeter at the waist level through the subject lying at decubitus position.

Most, but not all, menstruating women were studied during the early follicular phase of menstrual cycle. In a previous study it was reported that no difference was found in body composition or body fat distribution between premenopausal women studied in the luteal or follicular phase [5].

Systolic and diastolic blood pressures were measured on the right arm of the subject in an upright sitting position after at least 5 min rest using a mercury sphygmomanometer with appropriate cuff size. Two readings were recorded for each individual. The average of two readings was defined as the subject's blood pressure.

Blood samples were drawn between 8 am and 9 am after a 12- to 14-hour overnight fast for biochemical (glucose, uric acid, total and HDL cholesterol, triglyceride concentrations) determinations and basal insulin measurement. All biochemical analyses were performed using the Technicon DAX-72 autoanalyzer (Technicon, Bayer Corporation, Tarrytown, NY) in the Central Biochemistry Laboratory, Istanbul Faculty of Medicine. HDL cholesterol concentrations were measured using RA-XT autoanalyzer (Technicon, Bayer Diagnostics, Dublin) after phosphotungstic acid and magnesium chloride precipitation.

Insulin concentrations were measured by RIA using commercially available kits (Diagnostic Systems Laboratories, Webster, TX).

Insulin resistance was calculated by a computer derived formula [7]:

HOMA (homeostasis model assessment) = insulin (μ U/mL)/ $22.5 \times e^{-\ln(\text{fasting glucose mmol/L})}$

Intraabdominal fat volume (IAF) was calculated according to a previously validated formula [8]:

IAF (L) = $[(0.370 \times \text{abdominal sagittal diameter in cm}) - 4.85]$

Descriptive statistical results are presented in the tables as the means $\pm$ standard deviations. Since triglyceride, insulin and HOMA distributions significantly deviated from a normal distribution, measurements were log-transformed for analysis. However, since the difference in the results were extremely

small for between-groups comparisons, we presented the results using untransformed means $\pm$ standard deviations. Study subgroups were compared using Student's unpaired-t test. Significance was taken as $p < 0.05$.

The data of the subjects were recorded using "Dbase IV V2.0" (Borland International Inc., USA) software. All analyses were conducted by "SPSS/PC + V 3.0" statistical software (SPSS Inc., Chicago, IL) [9].

Results

The study parameters of pre- and postmenopausal BMI-matched women are summarized in Table 1.

Age, systolic and diastolic blood pressure, waist circumference, waist to hip ratio, and intraabdominal fat volume were significantly higher in postmenopausal women, even if BMI and body weight were matched. Fasting glucose, cholesterol, uric acid and triglyceride were significantly higher and HDL-cholesterol was significantly lower in postmenopausal women compared with premenopausals. No signifi-

cant differences were observed with respect to insulin levels and HOMA.

To determine the effects of age-related changes on the studied parameters, we selected different groups from the recorded data file of our outpatient obesity clinic according to the selection criteria. Basal insulin measurements and HOMA were not available for all patients in these groups. First, we identified premenopausal obese women with regular menstrual cycles and postmenopausal obese women matched for age. Study characteristics of these groups were summarized in Table 2. Total cholesterol concentrations were the single significantly different parameter between age-matched pre- and postmenopausal obese women. Second, we selected younger postmenopausal (≤ 50 years old) and older postmenopausal (> 50 years old) obese women with comparable BMI from recorded data file (Table 3). Age, systolic blood pressure, waist circumference, waist to hip ratio, glucose and uric acid concentrations were significantly higher in older postmenopausal obese women compared with younger postmenopausals. No statistically significant differences were evident with respect to diastolic blood pressure, hip circumference,

Table 1. Study parameters in pre- and postmenopausal body mass index-matched obese women

	Premenopausal n: 405	Postmenopausal n: 405	P
Age (years)	33.28 $\pm$ 7.62	52.36 $\pm$ 7.50	<0.001
Systolic blood pressure (mmHg)	135.12 $\pm$ 26.79	148.24 $\pm$ 29.77	<0.001
Diastolic blood pressure (mmHg)	87.70 $\pm$ 15.08	91.79 $\pm$ 15.71	<0.001
Weight (kg)	92.0 $\pm$ 17.5	91.2 $\pm$ 16.0	NS
Height (cm)	155.9 $\pm$ 5.3	155.6 $\pm$ 5.8	NS
BMI (kg/m ²)	37.83 $\pm$ 6.91	37.77 $\pm$ 6.84	NS
Waist circumference (cm)	99.19 $\pm$ 13.45	103.34 $\pm$ 13.20	<0.001
Hip circumference (cm)	123.10 $\pm$ 13.10	123.83 $\pm$ 13.09	NS
WHR	0.80 $\pm$ 0.07	0.84 $\pm$ 0.08	<0.001
IAF (L)	3.19 $\pm$ 1.42	3.97 $\pm$ 2.17	<0.001
Glucose (mg/dL)	99.41 $\pm$ 19.19	109.68 $\pm$ 33.62	<0.001
Uric acid (mg/dL)	4.34 $\pm$ 1.12	4.78 $\pm$ 1.47	<0.001
Cholesterol (mg/dL)	202.33 $\pm$ 37.09	232.22 $\pm$ 43.22	<0.001
HDL-cholesterol (mg/dL)	45.32 $\pm$ 10.89	47.24 $\pm$ 10.38	0.016
Triglyceride (mg/dL)	152.28 $\pm$ 74.93	172.68 $\pm$ 79.97	<0.001
Insulin (μ U/mL)	15.83 $\pm$ 10.96	17.36 $\pm$ 15.91	NS
HOMA	3.91 $\pm$ 2.74	4.81 $\pm$ 5.15	NS

BMI: body mass index; WHR: waist-to-hip ratio; NS: not significant

IAF: intraabdominal fat volume = $[(0.370 \times \text{abdominal sagittal diameter in cm}) - 4.85]$

HOMA (homeostasis model assessment) = $\text{insulin } (\mu\text{U/mL}) / 22.5 \times e^{-\ln(\text{fasting glucose mmol/L})}$

Table 2. Study parameters in pre-and postmenopausal age-matched obese women

	Premenopausal n: 212	Postmenopausal n: 212	P
Age (years)	45.54 ± 2.66	45.54 ± 2.66	NS
Systolic blood pressure (mmHg)	137.74 ± 26.25	140.12 ± 27.09	NS
Diastolic blood pressure (mmHg)	87.41 ± 15.06	88.66 ± 15.39	NS
Weight (kg)	88.73 ± 17.73	87.27 ± 17.09	NS
Height (cm)	155.9 ± 5.9	156.7 ± 5.8	NS
BMI (kg/m ²)	36.57 ± 7.46	35.58 ± 7.01	NS
Waist circumference (cm)	99.68 ± 14.13	99.54 ± 14.25	NS
Hip circumference (cm)	121.45 ± 14.24	120.68 ± 13.07	NS
WHR	0.82 ± 0.06	0.82 ± 0.07	NS
IAF (L)	3.92 ± 1.91	4.32 ± 1.70	NS
Glucose (mg/dL)	106.36 ± 36.24	104.84 ± 30.05	NS
Uric acid (mg/dL)	4.38 ± 1.27	4.66 ± 1.44	NS
Cholesterol (mg/dL)	217.55 ± 46.30	232.00 ± 49.50	<0.01
HDL-cholesterol (mg/dL)	45.48 ± 10.39	46.85 ± 10.68	NS
Triglyceride (mg/dL)	187.93 ± 210.40	187.56 ± 118.45	NS
Insulin (μU/mL)	19.83 ± 11.47	16.52 ± 15.94	NS
HOMA	5.20 ± 3.33	4.34 ± 4.84	NS

BMI: body mass index; WHR: waist-to-hip ratio; NS: not significant

IAF: intraabdominal fat volume = $[(0.370 \times \text{abdominal sagittal diameter in cm}) - 4.85]$

HOMA (homeostasis model assessment) = $\text{insulin } (\mu\text{U/mL}) / 22.5 \times e^{-\ln(\text{fasting glucose mmol/L})}$

Table 3. Study parameters in postmenopausal obese women ≤50 years and postmenopausal obese women >50 years

	Postmenopausal ≤50 years n: 257	Postmenopausal >50 years n: 337	P
Age (years)	46.04 ± 3.78	57.32 ± 5.33	<0.001
Systolic blood pressure (mmHg)	135.62 ± 33.82	144.08 ± 31.80	<0.01
Diastolic blood pressure (mmHg)	86.23 ± 19.46	87.89 ± 17.33	NS
Weight (kg)	90.08 ± 16.21	90.72 ± 17.47	NS
Height (cm)	155.8 ± 5.3	155.6 ± 5.8	NS
BMI (kg/m ²)	36.85 ± 6.85	37.75 ± 7.58	NS
Waist circumference (cm)	101.22 ± 13.33	105.15 ± 13.84	<0.001
Hip circumference (cm)	122.73 ± 13.01	123.46 ± 14.75	NS
WHR	0.82 ± 0.07	0.85 ± 0.07	<0.001
IAF (L)	4.31 ± 2.16	4.58 ± 5.50	NS
Glucose (mg/dL)	100.67 ± 27.46	112.52 ± 40.01	<0.001
Uric acid (mg/dL)	4.08 ± 1.88	4.73 ± 1.82	<0.001
Cholesterol (mg/dL)	222.20 ± 51.38	226.00 ± 49.84	NS
HDL-cholesterol (mg/dL)	45.51 ± 13.59	46.82 ± 14.87	NS
Triglyceride (mg/dL)	170.33 ± 94.11	162.76 ± 80.83	NS
Insulin (μU/mL)	16.34 ± 15.69	14.20 ± 10.52	NS
HOMA	4.37 ± 4.85	3.95 ± 3.88	NS

BMI: body mass index; WHR: waist-to-hip ratio; NS: not significant

IAF: intraabdominal fat volume = $[(0.370 \times \text{abdominal sagittal diameter in cm}) - 4.85]$

HOMA (homeostasis model assessment) = $\text{insulin } (\mu\text{U/mL}) / 22.5 \times e^{-\ln(\text{fasting glucose mmol/L})}$

intraabdominal fat volume, lipid profile, insulin measurements and HOMA.

Discussion

The changes in body composition and cardiovascular disease risk factors during menopausal transition are studied by several groups [3–6]. It is suggested that loss of ovarian function induces a reduction in resting metabolic rate, fat free mass and an increase in fat mass and abdominal adipose tissue accumulation [1]. These modifications contribute to the increased cardiovascular disease risk in postmenopausal women. Previous findings are supported by our study. In most of the previous reports non-obese subjects were studied [4, 5, 6]. It is interesting to determine whether obesity has influence on menopause-associated fat distribution and risk factor changes. McCrone *et al.* [10] reported that postmenopausal women with an early onset of obesity differed physiologically and psychologically from those with a late onset. In this study women with an early onset of obesity had significantly higher BMI and waist circumference. Alternatively Brochu *et al.* [11] reported the existence of a subgroup of obese but metabolically normal postmenopausal women who are insulin sensitive despite having a high accumulation of body fat. In this study, metabolically normal obese profile is associated with a lower accumulation of visceral adipose tissue and earlier (<20 year-old) age-related onset of obesity. According to Brochu's study, premenopausally obese women might be protected against the menopause transition-associated unfavorable changes compared with premenopausally lean women. Our findings favor the hypothesis that in obese women, menopause is associated with detrimental changes in body composition and risk factors even if BMI and body weight are maintained during menopause. Our study is not a longitudinal one but may partly answer the question of whether similar changes develop in obese postmenopausal women who maintain their premenopausal body weight during menopause transition. Although weight gain prevention is an important health goal during menopause period, menopause has already deleterious effects on obese women even if weight is maintained. Therefore weight loss should be particularly encouraged in obese premeno-

pausal women. Our findings may also suggest the previous observation that indicates the greater intraabdominal fat in postmenopausal women is independent of total adiposity [5].

Björkelund *et al.* [12] found that the menopause related increase in WHR was due to a decrease in hip circumference with no change in waist circumference indicating that menopause period was not associated with changes in abdominal adiposity. But in our study group the increase in WHR was originated from an increase in waist circumference in obese women representing a preferential increase in abdominal obesity.

In our study, although fasting glucose concentrations were higher in postmenopausal women, no significant differences were observed with respect to insulin levels and HOMA. Similar findings were observed by Zamboni *et al.* [3]. In their study, basal glucose and sum of glucose during oral glucose tolerance test were significantly higher in the postmenopausal women whereas basal insulin and sum of insulin during oral glucose tolerance test did not differ significantly. Lack of significant differences between insulin levels and HOMA cannot exclude the significant alterations between more direct measures of insulin sensitivity in pre- and postmenopausal women. However, assessment of insulin sensitivity by insulin clamp or other techniques is very difficult to achieve in a large series. Hyperuricemia is reported to be an inherent component of the metabolic syndrome and could be used as a simple marker for insulin resistance [13, 14]. In our study uric acid concentrations were significantly higher in postmenopausal women. In addition higher total cholesterol, blood pressure and lower HDL-cholesterol were observed in postmenopausal women with similar BMI. These differences could not be explained by the total body fat. Ageing may be responsible for these observations. The Framingham Heart Study reported that the change from premenopausal to postmenopausal status for women from the Framingham cohort followed for nine biennial examination was associated with an increase in total cholesterol level but no increase in blood pressure, glucose concentrations or body weight [15]. In another Framingham study, an increase was observed in total and LDL cholesterol concentrations but HDL and VLDL cholesterol concentrations did not change with age [16]. A further prospective study of Framingham cohort indi-

cated a rise in plasma total cholesterol and BMI and a decrease in HDL cholesterol among healthy young men and women during a 8-year follow-up [17]. Chang *et al.* [6] evaluated lean ($\text{BMI} < 30 \text{ kg/m}^2$) pre- and postmenopausal women. In their study, age exerted independent effects on post-oral glucose load plasma glucose concentrations, systolic and diastolic blood pressure, total and LDL-cholesterol concentrations. They concluded that through the ageing and menopausal effects, body fat content and central fat distribution will increase in lean women. Zamboni *et al.* [3] studied obese pre- and postmenopausal women. Their findings indicated that visceral abdominal adipose tissue areas increase with age. When we selected age-matched pre- and postmenopausal obese women, only total cholesterol concentrations were found to be significantly higher in the postmenopausals. When we selected relatively younger and older postmenopausal obese women, detrimental changes for systolic blood pressure, waist circumference, waist to hip ratio, glucose and uric acid concentrations were evident in the older postmenopausals. No significant differences were found between diastolic blood pressure, lipid profile and intra-abdominal fat volume in younger and older postmenopausal women, an outcome different from the data of premenopausal and postmenopausal BMI-matched obese women (Table 1). However, a trend for the increases in total cholesterol concentrations, intraabdominal fat volume and diastolic blood pressure was evident in older postmenopausal obese women. Our findings may indicate that in obese women, ageing through premenopausal and, in particular, postmenopausal time periods is an important factor to disclose detrimental changes in the postmenopausal stage even if BMI does not change. Kotani *et al.* [18] indicated that the increase in the relative visceral fat volume with age was about 2.6 times greater in postmenopausal obese ($\text{BMI} > 25 \text{ kg/m}^2$) women compared with premenopausals. In their study, no obvious difference in intraabdominal fat volume was found between pre- and postmenopausal women of similar age. In addition

Tremollieres *et al.* [4] showed that years since menopause, but not age, was a predictor of body fat mass and proportion of android fat in a relatively smaller study group composed of lean women. In their study young (< 60 years) and old (> 60 years) lean postmenopausal women were also studied. They found that absolute amount of fat and BMI were significantly increased in old postmenopausal women compared with young postmenopausals; however, proportion of android fat was not significantly different between young and old postmenopausal women. Alternatively, Toth *et al.* [5] showed that intra-abdominal fat remained significantly higher in early-postmenopausal lean women compared with middle-aged premenopausal lean women, even after statistical adjustment for age and total body fat mass. Differing results of these studies and our study could be explained by the variations in the populations studied and different characteristics of the study groups such as age and BMI. In addition, in the previously cited studies, abdominal fat mass was measured by computerized tomographic scans [5, 18] or dual x-ray absorptiometry [4], which are more precise methods to determine abdominal fat compared with anthropometry. In our study group, menopause transition is particularly associated with an adverse effect on total cholesterol concentrations, which is similar to the finding obtained from Framingham study [15]. Our findings may suggest that both ageing, particularly in the postmenopausal period, and menopause transition have adverse effects on body fat distribution and cardiovascular risk factors in obese women.

As a summary it can be suggested that an increase in intraabdominal fat accumulation and metabolic consequences of abdominal obesity disturb postmenopausal obese women even if total body weight and BMI do not change during menopause. Ageing, particularly throughout the postmenopausal years, appears to have important influences on the unfavorable changes associated with menopause transition in obese women.

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