Tohoku J. Exp. Med., 2004, **202**, 173-180

Orlistat, Sibutramine, or Combination Therapy: Which Performs Better on Waist Circumference in Relation with Body Mass Index in Obese Patients?

Neslihan Aydin, Pinar Topsever,[1] Ayça Kaya, Müzeyyen Karasakal, Celal Duman and Arslan Dağar

Department of Internal Medicine, Haydarpaşa Numune Teaching and Research Hospital, Istanbul, Turkey and
[1]Department of Family Medicine, Kocaeli University Faculty of Medicine, Kocaeli, Turkey

Aydin, N., Topsever, P., Kaya, A., Karasakal, M., Duman, C. and Dağar, A. *Orlistat, Sibutramine, or Combination Therapy; Which Performs Better on Waist Circumference in Relation with Body Mass Index in Obese Patients?* Tohoku J. Exp. Med., 2004, **202** (3), 173-180 —— The aim of this study was to evaluate decrease in waist circumference in obese patients receiving different anti-obesity treatments. The study was designed as a short-term (12 weeks), open-label, and randomized trial. Eighty six patients (70 females, 81.4%; mean age 41.09±8.73 years, mean BMI 36.1±4.3 kg/m^2) were randomized to four different therapy groups. The primary outcome parameters were waist circumference and body mass index (BMI). The therapy groups were a) diet+sibutramine 1×10 mg/d (n=22), b) diet+orlistat 3×120 mg/d (n=25), c) combination of diet+sibutramine+orlistat (n=20) and d) diet (n=19). Combination therapy was more effective than diet and orlistat mono-therapy (p<0.0001 for all), but not significantly superior to sibutramine mono-therapy (p=0.072) in decreasing BMI. Sibutramine mono-therapy was significantly more effective in inducing BMI decrease compared with orlistat mono-therapy (p=0.039). The association between change in BMI and change in waist circumference was strongest in the orlistat mono-therapy group (P interaction=0.003). This means that patients taking orlistat experienced more decrease in waist circumference (3.4 cm, R^2=0.29) per unit decrease in BMI compared to patients under combination therapy (2.6 cm, R^2=0.25, P interaction = 0.015) and patients taking sibutramine (1.8 cm, R^2=0.19, P interaction=0.026). In the diet therapy group decline in waist circumference was independent of BMI (1.9 cm, R^2=0.02, P interaction=0.076). Although combination therapy and sibutramine mono-therapy were more effective in

Received November 11, 2003; revision accepted for publication January 15, 2004.

Address for reprints: Pinar Topsever, Cetin Emec Bulvari, Suyani Sokak, Yali Apt. Nr 18/9, 81070 Suadiye, Istanbul, Turkey.

e-mail: topsever@superonline.com

This study was carried out at Haydarpasa Numune Teaching and Research Hospital, Istanbul, Turkey; no supports or grants were involved.

decreasing BMI, reduction in waist circumference and BMI was most significantly associated with the orlistat mono-therapy group. This may hint at the possibility of orlistat inducing weight loss mainly in the abdominal area targeted to reduce cardiovascular risk. ——— obesity; orlistat; sibutramine; waist circumference; cardiovascular risk factors

The prevalence of obesity is increasing worldwide leading to higher cardiovascular morbidity. Cardiovascular risk is known to be strongly associated with visceral obesity. The benefits of weight loss in terms of cardiovascular risk factors have been proven by many studies (Hubert et al.1983; Colditz et al. 1990; Turner 1992; Hauner 1995; Hodge et al. 2001; Tiengo et al. 2001; Harvey et al. 2002). Visceral adipose tissue contributes significantly to the metabolic complications of obesity and its cardiovascular risk (Van Gaal et al. 1988, 1998; Despres 1993). The gold standard for assessing abdominal adipose tissue is computerized tomography or magnetic resonance imaging. In the past the "waist/hip ratio" was used as a surrogate marker for abdominal adiposity but it has been replaced with the simpler and more reliable measurement of waist circumference (Lean 1998). Obesity management is based on lifestyle modifications including development of diet and exercise habits. Although diet and exercise are the cornerstones of any weight loss intervention, unfortunately they seldom prove to be effective, especially over long-term. In patients where lifestyle changes are ineffective, drug therapy may be indicated. Presently two anti-obesity drugs are available on the market. Orlistat, with a peripheral mode of action, is inducing weight loss by selectively inhibiting gastrointestinal lipase activity, thereby reducing the absorption of dietary fat by approximately one third. The second drug is sibutramine, a serotonin and noradrenalin reuptake inhibitor, which induces weight loss by enhancing satiety and increasing metabolic rate. There are numerous studies about the effect of sibutramine (Van Gaal et al. 1998; Cuellar et al. 2000; Gökcel et al. 2000, 2002; McMahon et al. 2000; Wirth and Krause 2001; Serrano-Rios et al. 2002) or orlistat (Zavoral 1998; Hauptmann 2000; Broom et al. 2002; Gökcel et al. 2002) on waist circumference. But there are no comparative studies on the efficacy of sibutramine, orlistat and the combination of both drugs.

Our aim in this study was to compare the effects of orlistat, sibutramine and combination therapy on waist circumference in obese patients.

Subjects and Methods

The local ethical committee approved the study protocol, which was designed according the Declaration of Helsinki. All participants gave their verbal informed consent. The study was designed as a prospective, randomized, parallel, and open-label trial. Patients were recruited in the internal medicine outpatient clinic unit of a State Hospital. Inclusion criteria were age over 18 and under 60 years, history of at least one unsuccessful attempt to lose weight by dietary measures in the past, being naive to either of the drugs and a body mass index of $\geqq$30 kg/m^2. As a proof of alimentary exogenous obesity, patients who had lost at least 2.5 kg of initial weight with a medium low calorie diet of 1200-1500 kcal/day during a preceeding run-in period of 4 weeks were eligeable for the study.

Exclusion criteria were endocrine obesity, hypercortisolism being investigated via assessment of free cortisol in a 24 hour urine sample in patients who were suspected of Cushing Syndrome (Thorner et al. 1998), thyroid dysfunction defined by T_4, TSH serum levels (Larsen et al. 1998), uncontrolled hypertension defined by JNC criteria (Joint National Committee

TABLE 1. *Baseline characteristics of the study population by therapy groups*

	Age (years)	Gender (f/m)	BMI (kg/m^2)	WC (cm)
Sibutramine (n=22)	40.3±9	17/ 5	35.5±4.4	103.3±12.5
Orlistat (n=25)	43.9±8.8	21/ 4	35.5±4.3	104.2±15.2
Combination (n=20)	41.8±8.8	15/ 5	37.8±4.7	110.2±14
Diet (n=19)	37.5±7.3	17/ 2	35.7±3.8	97.9±11.8
Total (n=86)	41.1±8.7	70/16	36.1±4.3	103.9±13.9

BMI, body mass index; WC, waist circumference.

TABLE 2. *BMI decrease and waist circumference decline by therapy groups*

	BMID* (kg/m^2)	WCD** (cm)
Sibutramine (n=22)	–4.4±1.3	–13.5±4.8
Orlistat (n=25)	–3.6±1	–14.0±5.9
Combination (n=20)	–5.1±1.4	–16.7±7.0
Diet (n=19)	–2.5±1.3	– 8.4±9.5
Total (n=86)	–3.9±1.5	–13.2±6.8

BMID, decrease in body mass index; WCD, decline in waist circumference.

Differences in means between groups significant at $^{*}p$=0.001, $^{**}p$=0.003 levels using one-way analysis of variance (ANOVA).

1997), known history of diabetes mellitus defined by patient history and/or antidiabetic therapy, pregnancy verified by β-HCG serum levels (Carr et al. 1998), and lactation. Women of reproductive age were enrolled only under the condition of proof of using a safe and medically accepted contraceptive method.

A total of 104 outpatients of the department of internal medicine, fulfilling the above mentioned eligibility criteria, upon their informed consent, were initially enrolled (16 males and 70 females, mean age 41.1±8.7 years, mean BMI 36.1±4.3 kg/m^2).

The study group was randomly divided into 4 different treatment groups by means of lottery. All groups received the same dietary restrictions consisting of a standard composition, medium low calorie diet (i.e., 1200 kcal/day for women and 1500 kcal/day for men) and a medium exercise programme recommending one hour walks every second day (National Institute of Health 1998).

Furthermore, the first group received 10 mg sibutramine p.o. once daily, the second group received 120 mg orlistat p.o. three times daily, the third group received 10 mg sibutramine p.o. once daily and 120 mg orlistat p.o. three times daily and the fourth group received dietary restriction and exercise programme only.

At baseline a detailed anamnesis was assessed. All patients also underwent a careful physical examination. Patients were followed up every two weeks for body weight (in order to calculate body mass index) and waist circumference. The total follow up duration was 12 weeks. Body weight was assessed in the morning fasting state by an electronical weight scale. Body mass index was calculated as weight in kilograms divided by the square of height in meters. Waist circumference was measured at the midline between arcus costarum and crista iliaca superior. Patients who failed to attend the clincial appointments or suffered from severe adverse events were exluded. Serious adverse events were defined as those adverse events which required hospitalization, were life threatening or resulted in a persistent or significant disability or death.

Statistical analysis was performed on the data of 86 study completers with SPSS 11.5 for Windows (SPSS Inc., Chicago, IL, USA), using descriptive statistics with all values given as mean±S.D. Student t-test and oneway analysis of variance (ANOVA) were chosen for between group comparisons of unpaired

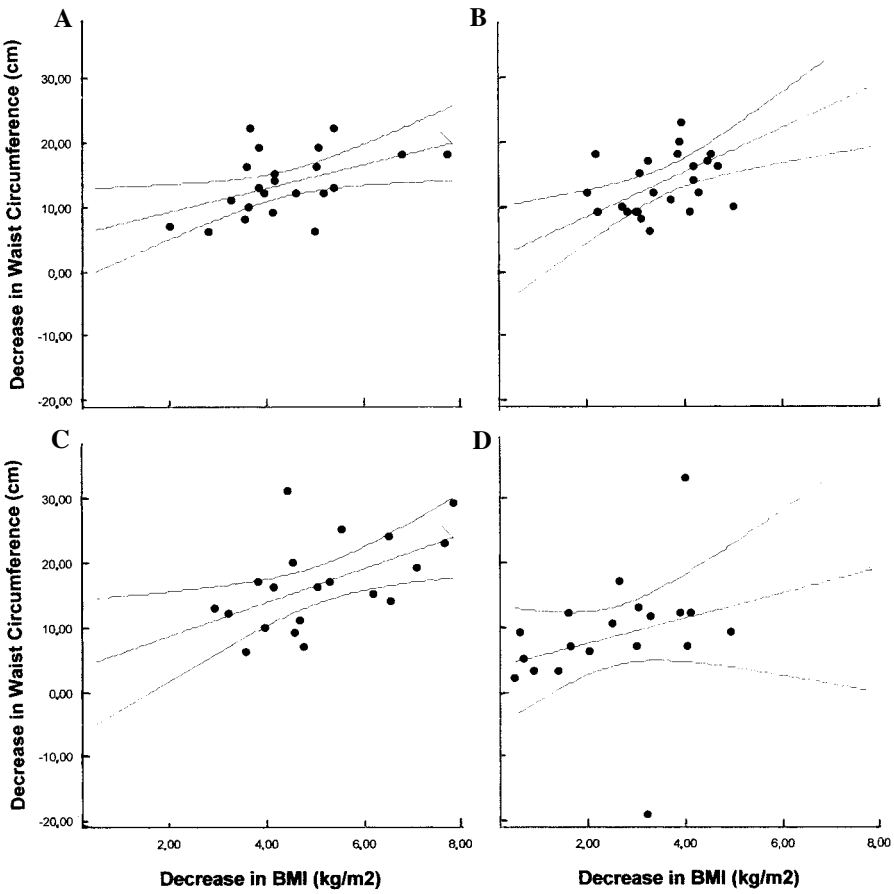

Fig. 1. Relationship of decline in waist circumference and body mass index by therapy
A: Sibutramine (WCL, cm=5.55+1.81 *bmiloss), B: Orlistat (WCL, cm=1.63+3.41 *bmiloss), C: Combination (WCL, cm=3.40+2.60 *bmiloss), D: Diet (WCL, cm=3.57+1.93 *bmiloss).

parametric samples. Linear correlation of parametric samples was assessed calculating the Pearson correlation coefficient. The associations between waist circumference and therapy regimen were inverstigated by multiple linear regression analyses, with waist circumference as the dependent variable and therapy group as the independent variable. Possible associations between therapy regimen and BMI in the association of therapy regimen with change in waist circumferences were assessed by using interaction terms in multiple regression analyses. The significant level was 0.05 with an assumed confidence interval of 95%.

Results

The therapy groups matched for age, sex, body mass index and waist circumference. Thus the randomization was considered successful. The baseline characteristics of the study population are shown in Table 1.

BMI decrease was significantly differing between groups (p=0.001), being highest in the combination therapy group, followed by sibutramine mono-therapy, orlistat mono-therapy and diet therapy (Table 2).

With −16.70±6.98 cm, the combination therapy group produced greatest change in waist circumference. Even though, orlistat mono-therapy was less effective on body mass index, it

proved to reduce waist circumference as effective as sibutramine mono-therapy (−14.04±5.88 cm vs. −13.54±4.83 cm, p=0.806) (Table 2).

Correlations between decrease in body mass index (kg/m^2) and waist circumference (cm) were significant for all groups, except for the diet therapy group. Changes in body mass index and waist circumference were best correlating in the orlistat mono-therapy group (r=0.563, p=0.003), followed by the combination therapy group (r=0.537, p=0.015) and the sibutramine mono-therapy group (r=0.474, p=0.026).

Multiple regression analysis revealed a decrease of 1.8 cm in waist circumference per unit decrease in body mass index in the sibutramine mono-therapy group. In this therapy group, the association of body mass index and therapy regimen was significant (P interaction =0.026, adjusted R^2=0.19). In the orlistat mono-therapy group, each unit decline in BMI resulted in 3.4 cm decrease in waist circumference. Again, the association of change in BMI and therapy regimen was significant (P interaction=0.003, adjusted R^2 =0.29). In the combination therapy group, each unit change in BMI accounted for 2.6 cm decrease in waist circumference. This effect was also associated with decrease in BMI (P interaction 0.015, adjusted R^2=0.25).

In the diet therapy group, each unit change in BMI accounted for 1.9 cm decrease in waist circumference. This effect was independent of decrease in BMI (P interaction 0.076, adjusted R^2=0.02) (Fig. 1).

Discussion

Although obesity is generally characterized by an excess accumulation of body fat, location of body fat is a crucial determinant in terms of metabolic and cardiovascular risk. Visceral obesity is known to show a closer correlation with dyslipidemia, hyperinsulinemia, higher risk of diabetes mellitus and cardiovascular events, than total accumulated body fat mass (Tschernoff et al. 2000). Waist circumference is a marker of visceral obesity, which has also been shown to be a reliable indicator for cardiovascular risk (Larsen et al. 1998; National Institute of Health 1998).

In this study, we aimed to compare the effects of different anti-obesity treatment regimens on waist circumference in relation to changes in body mass index. Several studies have been conducted with each of the anti obesity drugs, but there are no studies which directly compare the effects of orlistat, sibutramine and their combination in terms of waist circumference.

Here we show that sibutramine, orlistat or their combination, regardless of possible interactions with changes in body mass index, are more beneficial in reducing waist circumference compared to non-pharmaceutical interventions. Many studies conducted with each of these drugs have shown similar results. Several studies of diabetic as well as non-diabetic obese patients have revealed a significant beneficial effect of sibutramine on waist circumference. However, in these studies sibutramine was used in different doses and for a longer period of time (Lean 1997; Cuellar et al. 2000; Fanhaenel et al. 2000; Fujioka et al. 2000). Another study, featuring 36 patients taking sibutramine, revealed a significant decrease in intra-abdominal adipose tissue, which was correlated with changes in weight and BMI for both genders (Kamel et al. 2000). They showed that in women, changes in intra-abdominal adipose tissue were also significantly correlated with decrease in waist circumference and waist/hip ratio. Energy intake and sibutramine dose in their study were very similar to our study design, but sibutramine was administered for a duration of 6 months which was twice as long compared to our study (Kamel et al. 2000). In the prospective, open–label clinical study enrolling 50 uncomplicated obese patients with a 6 months 10 mg sibutramine treatment, Wauters et al. (1997) have shown a significant intra-group reduction in waist circumference. Likewise, a meta-analysis of four long-term, randomized, double-blind, placebo-controlled, parallel group trials showed that sibutramine significantly reducted weight and waist circumference (Van Gaal et al. 1998).

There are a few long-term, double-blind, randomized controlled trials, investigating the effects of orlistat on waist circumference in diabetic as well as in non-diabetic obese patients (Hollander et al. 1998; Zavoral 1998; Kamel et al. 2000). These all reported a significant beneficial effect of orlistat compared to placebo. There is no paper in the current medical literature comparing the effects of sibutramine, orlistat or their combination on waist circumference. There is only one study conducted by Gökcel et al. (2002), where sibutramine, orlistat or metformin was given during a period of six months to 150 obese patients. They found significant intra-group differences of baseline and endpoint waist circumference for each drug used. Sibutramine was found to be most effective in reducing waist circumference, followed by metformin and orlistat. However, sibutramine was applied in a higher dose of two times 10 mg per day and there was no inter-group comparison on the efficacy on waist circumference of the drugs.

In our study, sibutramine mono-therapy performed significantly better in weight management compared with orlistat. But when examining the decrease in waist circumference, orlistat mono-therapy seemed to be equally effective to sibutramine mono-therapy (Table 2). Waist circumference declines of patients under orlistat mono-therapy showed the highest positive correlation with decrease in body mass index, which translates into most efficient waist circumference decrease per unit change in weight induced by this drug. Accordingly, orlistat mono-therapy had the highest predictive value on the change in waist circumference, compared to the other therapy groups. On the other hand, sibutramine mono-therapy displayed the lowest predictive value on waist circumference changes.

Combination therapy, which proved highly effective in reducing body mass index, did not show the same performance in terms of decreasing waist circumference, suggesting that of the enhancing effect of orlistat therapy on decrease in waist circumference was blunted by sibutramine.

Conclusion: There are no studies in the current medical literature comparing the effect of different anti obesity drugs on the relationship of weight loss and waist circumference. In this study, orlistat mono-therapy seemed to best correlate decrease in body mass index with waist circumference reduction, which translates into weight loss in the targeted abdominal area known to account for metabolic and cardiovascular risk. However, when interpreting the results of the present study, the small sample size in the individual therapy groups, as well as the complicated and unclear different pharmacological mechanisms of action of the two investigated anti obesity drugs should be taken into consideration.

References

Broom, I., Wilding, J., Stott, P. & Myers, N. (2002) Randomised trial of the effects of orlisat on body weight and cardiovascular disease risk profile in obese patients: UK Multimorbidity Study. *Int. J. Clin. Pract.,* **56,** 494-499.

Carr, B.R. (1998) Disorders of the Ovaries and Female Reproductive Tract; Section 5. In: *Williams Textbook of Endocrinology*., edited by J.D. Wilson, D.W. Foster, H.M. Kronenberg & P.R. Larsen. WB Saunders Philadelphia, pp. 751-817.

Colditz, G.A., Willer, W.C., Stampfer, M.J., Manson, J.E., Hennekens, C.H., Arky, A. & Speizer, F.E. (1990) Weight as a risk factor for clinical diabetes in women. *Am. J. Epidemiol.*, **132**, 501-513.

Cuellar, G.E., Ruiz, A.M., Monsalve, M.C. & Berber, A. (2000) Six month treatment of obesity with sibutramine 15 mg; a double-blind, placebo-controlled monocenter clinical trial in a Hispanic population. *Obes. Res.,* **8**, 71-82.

Despres, J.P. (1993) Abdomial obesity as an important component of the insulin Resistance syndrome. *Nutrition,* **9,** 452-459.

Fanhaenel, G., Cortinas, L., Sanchez-Reyes, L.& Berber, A. (2000) A clinical trial of the use of Sibutramine for the treatment of patients suffering essential obesity. *Int. J. Obes.*, **24**, 144-150.

Fujioka, K., Seaton, T.B., Rowe, E., Jelinek, C.A., Raskin, P., Lebowitz, H.E., Weinstein, S.P. & the Sibutramine/Diabetes Clinical Study Group. (2000) Weight loss with sibutramine improves

glycemic control and other metabolic parameters in obese patients with type 2 diabetes mellitus. *Diabetes Obes. Metab.,* **2,** 175-187.

Gökcel, A., Karaköse, H., Ertörer, E.M., Tanaci, N., Tütüncü, N.B.& Güvener, N. (2001) Effects of sibutramine in obese female subjects with type 2 diabetes and poor blood glucose control. *Diabetes Care*, **24,**1957-1960.

Gökcel, A., Gümürdülü, Y., Karaköse, H., Ertörer, E.M., Tanacı, N., Tütüncü, N.B.& Güvener N. (2002) Evaluation of the safety and efficacy of sibutramine, orlistat and metformin in the treatment of obesity. *Diabetes Obes. Metab.,* **4,** 49-55.

Harvey, E.L., Genny, A.-M., Kirk, S.F.L. & Summerbell, C.D. (2002) An updated systematic review of interventions to improve health professionals' management of obesity. *Obesity Reviews*, **3,** 45-55.

Hauner, H. (1995) Abdominal obesity and coronary heart diesease. Pathophysiology and clinical significance. *Herz*, **20,** 47-55.

Hauptman, J. (2000) Orlistat: selective inhibition of caloric absorption can affect long term body weight. *Endocrine,* **13**, 201-206.

Hodge, A.M., Courtenand, M.P. & Zimmet, P. (2001) Obesity and Type 2 Diabetes Mellitus. In: International Textbook of Obesity. Edited by Björntorp, P., John Wiley & Sons, Ltd., Chichester, UK, pp. 351-364.

Hollander, P.A., Elbein, S.C., Hirsch, I.B., Kelley, D., McGill, J., Taylor, T., Weiss, S. R., Crockett, S.E., Kaplan, R.A., Comstock, J., Lucas, J.P., Lodewick, P.A., Canovotchel, W., Chung, J. & Hauptmann, J. (1998) Role of Orlistat in the treatment of obese patients with type 2 diabetes. *Diabetes Care*, **21,** 1288 -1294.

Hubert, H.B., Feinleib, M., McNamara, P.M. & Castelli, W.P. (1983) Obesity as independent risk factor for cardiovascular disease: A 26-year follow-up of participants in the Framingham Heart Study. *Circulation*, **67,** 968-977.

Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (1997) The sixth Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure. *Arch. Intern. Med.,* **157,** 2413- 2446.

Kamel, E.G., McNeill, G. & Van Wijk, M.C. (2000) Change in intra-abdominal adipose tissue volume during weight loss in obese men and women: correlation between magnetic resonance imaging and anthropometric measurements. *Int. J. Obes. Relat. Metab. Disord.,* **24**, 607-613.

Larsen, P.R., Davies, T.F. & Hay, I.D. (1998) The Thyroid Gland. In: *Williams Textbook of Endocrinology*, edited by J.D. Wilson, D.W. Foster, H.M. Kronenberg and P.R. Larsen. WB Saunders, pp. 389-515.

Lean, M. (1997) Sibutramine- a review of clinical efficacy. *Int. J. Obes.,* **21**, 530-536.

Lean, M. (1998) Clinical Handbook of Weight Management. Martin Dunitz Ltd., London, pp. 3-16.

McMahon, F.G., Fujioka, K., Singh, B.N., Mendel, J.M., Rowe, E., Rolston, K., Johnson, F. & Mooradian, A.D. (2000) Efficacy and safety of sibutramine in obese white and African American patients with hypertension: a 1-year, double-blind, placebo-controlled, multicenter trial. *Arch. Intern. Med.,* **160**, 2185-2191.

National Institutes of Health, National Heart, Lung, and Blood Institute (1998) Clinical Guidelines on the Identification, Evaluation and Treatment of Overweight and Obesity in Adults. Evidence Report. *NIH PUBLICATIONS*, No. 98-4083, USA, pp. 57-80.

Serrano-Rios, M., Melchionda, N. & Moreno-Carretero, E. (2002) Role of Sibutramine in the treatment of obese Type 2 Diabetes Mellitus diabetic patients receiving sulphonylurea therapy. *Diabet. Med.*, **19,** 119-124.

Thorner, M.O., Vance, M.L., Laws, E.R., Jr., Hovarth, E. & Kovacs, K. (1998) The Anterior Pituitary. In: *Williams Textbook of Endrocrinology*, edited by Wilson, J.D., Foster, D.W., Kronenberg, H.M., Larsen , P.R., WB Saunders, Philadelphia, pp. 249-340.

Tiengo, A. & Avogaro, A. (2001) Cardiovascular Disease. In: *International Textbook of Obesity*, edited by P. Björntorp, John Wiley&Sons Ltd., Chichester, UK, pp. 365-377.

Tschernof, A. & Despres, J.P. (2000) Obesity and Lipoprotein Metabolism. In: *Clinical Obesity*. edited by P.G. Kopelman & M.J. Stock. 1st Turkish Ed., Blackwell Science Limited, Oxford, pp. 177-205.

Turner, R.C. (1992) The role of obesity in diabetes. *Int. J. Obes.,* **16,** Suppl. 2, 43-46.

Van Gaal, L., Rillaerts, E., Creten, W. & Leeuw, L. (1988) Relationship of body fat distribution pattern to atherogenic risk factors in non insulin dependent diabetes. Preliminary results. *Diabetes Care*, **11,** 103-106.

Van Gaal, L.F., Wauters, M.A., Pfeiffer, F.W. & De Leeuw, I.H. (1998) Sibutramine and fat distribution: is there a role for pharmacotherapy in abdominal/visceral fat reduction? *Int. J. Obes.,* **22,** Suppl. 1, 38-40.

Wauters, M., Pfeiffer, F., Gubbels, N., Van De Sompel, A. M., Corthouts, R., De Schepper, A., De Leeuw, I. & Van Gaal L. (1997) Visceral fat decreases after six months treatment with sibutramine in obese subjects. *Int. J. Obes.,* **21,** Suppl. 2, 55.

Wirth, A. & Krause, J. (2001) Longterm weight loss with sibutramine: a randomized controlled trial. *JAMA,* **286**, 1331-1339.

Zavoral, J. H. (1998) Treatment with orlistat reduces cardiovascular risk in obese patients. *J. Hypertens*, **16,** 2013-2017.