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Weight loss with very-low-calorie diet and cardiovascular risk factors in moderately obese women: One-year follow-up study including ambulatory blood pressure monitoring

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OBJECTIVE: The beneficial effects of weight loss with a very-low-calorie diet (VLCD) on cardiovascular risk factors have been reported at the end of energy restriction. As the effects, especially on blood pressure, may not remain constant during weight maintenance, we studied the longer-term effects of weight loss on 24 h ambulatory blood pressure (ABP), lipids, glucose and insulin.
DESIGN: Prospective study of a 17-week weight loss programme containing an eight-week VLCD period and follow-up visit at one-year.
SUBJECTS: Twenty-nine moderately obese, normotensive or mildly hypertensive women. The mean ± s.d. body mass index (BMI) was 36.0 ± 2.6 kg/m^2 and mean age 40.3 ± 8.3 y.
RESULTS: In the last week of the VLCD, the mean (s.d.) weight loss was 12.4 ± 3.3 kg ($P < 0.001$), at the end of the programme 15.1 ± 4.4 kg ($P < 0.001$ *vs* baseline), and at one-year follow-up 10.7 ± 7.6 kg ($P < 0.001$ *vs* baseline). Mean 24 h ABP decreased 8.0/4.6 mmHg ($P < 0.001$ for both) on the last week of the VLCD, at the end of the programme, the systolic ABP decrease was 4.7 mmHg ($P < 0.01$ *vs* baseline) and diastolic 2.1 mmHg (not statistically significant (NS) *vs* baseline). At one-year follow-up, the mean systolic ABP decrease was 4.1 mmHg ($P < 0.01$ *vs* baseline) and mean diastolic 3.0 mmHg ($P < 0.05$ *vs* baseline). Sodium excretion decreased 55 mmol/24 h in the last VLCD week ($P < 0.01$) and returned to baseline after that. At the one-year follow-up, beneficial changes, compared with baseline, were observed in mean serum glucose (−0.28 mmol/l, $P < 0.05$), triglyceride (−0.35 mmol/l, $P < 0.01$) and HDL cholesterol (+0.16 mmol/l, $P < 0.001$).
CONCLUSIONS: This weight loss programme with a VLCD enabled obese subjects to lose weight and decrease cardiovascular risks. Despite some regain in weight during follow-up, the beneficial effects were overall maintained over the year. Sodium intake tended to increase during follow-up. Information on sodium restriction should be included in weight loss programmes.

Keywords: obesity; weight loss; very-low-calorie diet; ambulatory blood pressure; sodium; cardiovascular risk factors

Introduction

Obesity is associated with several health risks, including increased risk for cardiovascular diseases and mortality.[1,2] These risks are partly mediated by elevated blood pressure (BP), lipids and glucose.[1,2] In primary prevention and first step non-pharmacological treatment of hypertension, weight reduction and sodium restriction are recommended.[3,4] Weight loss has beneficial effects on other risk factors as well.[5,6]

During weight loss with a very-low-calorie diet (VLCD), a rapid decrease in BP, both in hypertensive and normotensive, obese subjects has been reported previously,[7,8] and this seems to be independent of sodium intake.[7] The role of sodium restriction on BP during less severe energy restriction is controversial.[9]

Compared to casual BPs, more reproducible pressures can be measured by non-invasive 24 h ambulatory blood pressure (ABP) monitoring. These values correlate more closely with end-organ damage than casual pressures.[10] ABP monitoring is largely without placebo effect[11] and lacks observer bias.

We report here changes in weight, ABP monitoring, casual BPs, urinary sodium excretion, serum lipids, glucose and insulin, during a 17-week weight loss programme that combined an eight-week VLCD period with life-style modification in normotensive and mildly hypertensive moderately obese women. Furthermore, we extended the monitoring of these risk factors to the one-year follow-up visit.

Subjects

The subjects were recruited by an advertisement in a magazine seeking obese persons to participate in an

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obesity treatment study using a medically supervised VLCD programme. The criteria for the study were: age, 20–60 y; stable weight during the preceding two months; body mass index (BMI), 32–40 kg/m^2 and no diagnosis of hypertension or diabetes or any other major diseases.

The 17-week weight reduction programme included an eight-week period of VLCD followed by a gradual change (refeeding) to low-energy food. During twelve group sessions, behaviour methods for weight control were taught. This programme has been described elsewhere.[12] No instructions were given concerning sodium intake. Subjects were encouraged to increase their exercise to the equivalent of a 30 min walk daily. Physical activity was not assessed during the programme or follow-up. The cardiovascular risk factors were reassessed one year after treatment initiation.

Female study participants in Turku, 29 women, were included in this substudy. The mean age of the women was 40.3 y (s.d. 8.3), mean weight (96.1 kg (s.d. 10.9) and mean BMI 36.0 kg/m^2 (s.d. 2.6). Five subjects were mildly hypertensive at baseline (casual diastolic BP > 90 mmHg).

Methods

Blood pressure

ABP monitoring and casual measurements were performed four times during the study: at baseline, during the last week of the VLCD (week 8), during the last week of the weight loss programme (week 17) and one year after initiation of the treatment (week 52).

ABP was measured with Accutraker II devices (Suntech Medical Instruments, Raleigh, USA). During daytime (from 06.00–23.00 h) recorders were programmed to obtain measurements at intervals of 15 min, and during night-time (from 23.00–06.00 h) every 30 min. A cuff with a bladder width of 13 cm was used for subjects with an arm circumference of 35 cm or less and a cuff with a bladder width of 15 cm for subjects with an arm circumference above 35 cm. The editing criteria considered for deletion of readings from the recordings were: 1) Systolic pressure was below 60 mmHg or above 250 mmHg; 2) Diastolic pressure was < 35 mmHg or > 140 mmHg; and 3) Pulse was below 40 bpm or above 200 bpm. The recording was accepted as valid, when the rate of deleted readings was < 20%. The mean daytime and night-time BPs were calculated separately and the variable reading frequencies were taken into account for the 24-h values.

Casual measurements were taken by mercury sphygmomanometer after 10 min rest at 5 min intervals from the right arm by a trained observer. Korotkoff phase I and V sounds were used for systolic blood pressure (SBP) and diastolic blood pressure (DBP) measurements. The average of two readings was recorded. The cuff size was 42 cm × 15 cm for all.

Anthropometry and body composition

Weight was measured at each visit to the nearest 0.1 kg with the subject wearing indoor clothing without shoes. Waist–hip ratio (WHR) was calculated using circumferences measured midway between the costal arch and the iliac crest, and at the symphysis-trochanter femoris level. Percentage of body fat was measured using the bioelectrical impedance method (BIA-101A/S & spectrum, RJL systems, MI) and calculated according to the manufacturer's formula.

Biochemistry

All blood samples were taken after a 12 h fast, at the same time points as BP measurements. Serum cholesterol (CHOD-PAP) and triglycerides (GPO-PAP) were determined with fully enzymatic spectrophotometric reagent kits (Merck Diagnostica, Darmstadt, Germany). The serum HDL fraction was separated by precipitating VLDL and LDL with dextran sulphate 500 000,[13] and HDL cholesterol was analysed enzymatically from the supernatant. Serum glucose concentration was analysed spectrophotometrically, utilizing a glucose dehydrogenase based kit (Merck Diagnostica). Serum insulin concentration was measured with the aid of microparticle enzyme immunoassay (MEIA) technology (Abbott IMX analyzer and MEIA kit, Abbott Laboratories, Abbott Diagnostics Division, Abbott Park, IL 600641, USA). Urine sodium and potassium levels were analysed with ion-selective electrodes (Kone Microlyte, Kone Instruments, Espoo, Finland).

VLCD

The VLCD preparation used was Nutrilett^R (Nycomed Pharma AS, Oslo, Norway). The daily dose was five sachets and this contained 429 kcal/1759 kJ of energy, 60 g of protein, 7 g of fat and 30.5 g of carbohydrate, of which 17.5 g was fiber. The VLCD preparation was in powder form and was mixed with water. The VLCD included one daily tablet containing the recommended daily amounts of vitamins, minerals and trace elements, and one capsule containing essential fatty acids. The daily dose contains 3–5 g of sodium chloride. Addition of sodium chloride was permitted during the VLCD period.

The VLCD preparation and the whole programme was free of charge for the subjects. The subjects gave written informed consent before the start of treatment. The Ethics Committee of the Third Department of Medicine in Helsinki University Hospital approved the study protocol.

Statistical analysis

The statistical analysis was performed using the BMDP software.[14] The changes within the group were analysed with Student's one sample *t*-test.

Non-parametric tests were used in the case of skewed distributions. The Bonferroni procedure was used to assess statistically significant changes. Correlations were calculated with Pearson's correlation coefficients. Multivariate regression analysis was used to describe which factors contributed to changes in the risk factors during the weight loss programme and follow-up.

Results

Weight and fat distribution

One subject discontinued after the VLCD period, and another during the one-year follow-up. Table 1 and Figure 1 show that most of the weight loss occurred during the VLCD. At the end of the programme, the mean weight loss, as a percentage of initial weight, was 16%, and at the one-year follow-up visit 11%. The patients regained about one-third of their mean weight loss (4.4 kg of a 15.1 kg loss) during the follow-up. At the one-year visit, 14 patients (52%) were 10% or more below their baseline weight, while four patients (15%) had regained weight back to or above their baseline weight. WHR and waist circumference decreased significantly during treatment and significant change persisted for waist circumference at the one-year follow-up (Table 1).

Blood pressure

Table 2 and Figure 1 show BP results. In casual measurements, BP fell significantly from baseline during consumption of VLCD and during refeeding, and returned to baseline levels at the one-year follow-up. BP decreased during weight loss in all five subjects who were mildly hypertensive at baseline. At the follow-up visit, BP was mildly increased in three of them, despite good maintenance of weight loss in two of them. No one used antihypertensive medication during treatment or was using it at one-year follow-up.

With ambulatory monitoring, the largest BP decreases were observed during the VLCD. At the end of the treatment, systolic daytime and 24 h mean ABPs were significantly decreased from baseline. At the one-year visit, significant decreases in night-time and 24 h mean ABPs were observed.

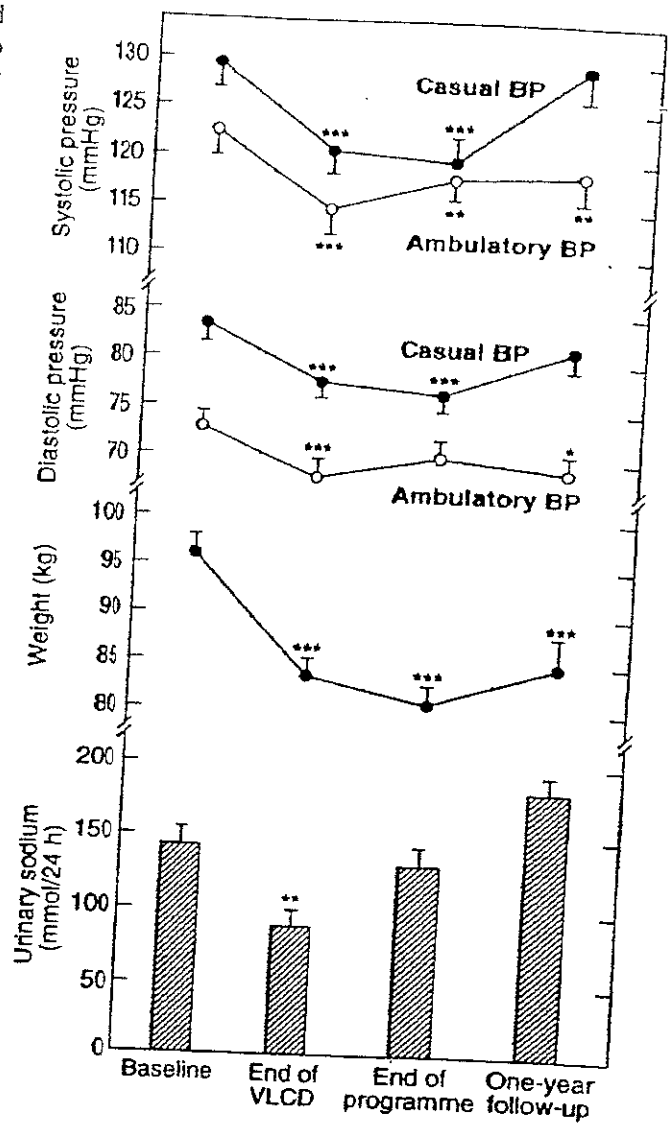

Figure 1 Mean (s.e.m.) casual and 24 h mean ambulatory blood pressure (BP), weight and urinary sodium excretion at baseline, at the end of the very low calorie diet (VLCD) period, at the end of the weight loss programme and at the one-year follow-up. ***$P < 0.001$, **$P < 0.01$, *$P < 0.05$ compared with baseline.

Biochemistry

During the VLCD, insulin, glucose, cholesterol, HDL cholesterol and triglycerides fell significantly. The decrease in glucose and triglycerides, and increase in HDL cholesterol, remained significant over the one-year period (Table 3). Urinary excretion of sodium in

Table 1 Mean baseline variables and changes from baseline during (week 8) and after (week 17 and 52) the weight loss programme

	n	*Baseline*	*n*	*Week 8*	*n*	*Week 17*	*n*	*Week 52*
Weight (kg)	29	96.1 (10.9)	29	−12.4 (3.3)***	28	−15.1 (4.4)***	27	−10.7 (7.6)***
BMI (kg/m^2)	29	36.0 (2.6)	29	−4.6 (1.1)***	28	−5.7 (1.5)***	27	−3.9 (3.0)***
Waist/hip	28	0.85 (0.04)	28	−0.03 (0.03)***	28	−0.03 (0.04)***	26	−0.02 (0.05)
Waist (cm)	28	103.7 (7.1)	28	−11.3 (3.5)***	28	−13.8 (4.7)***	26	−11.9 (8.6)***
Fat (%)	28	42.0 (4.1)	28	−4.2 (2.2)***	28	−6.3 (3.3)***		not done
U-Na (mmol/24 h)	29	142.8 (59.4)	29	−55.0 (79.5)**	28	−11.6 (75.6)	26	+42.5 (95.9)
U-K (mmol/24 h)	29	68.0 (20.7)	29	+12.8 (30.4)	28	+7.4 (31.8)	26	+21.2 (33.8)*

Values are means (s.d.). *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ compared with baseline and using the rule of Bonferroni.
BMI = body mass index; U-Na = urinary sodium excretion; U-K = urinary potassium secretion.

Table 2 Mean casual and ambulatory blood pressures at baseline and changes from baseline during and after the weight loss programme

	Baseline	*Week 8*	*Week 17*	*Week 52*
Systolic pressure (mmHg)				
Casual	129.6 (15.1)	−9.1 (7.4)***	−10.2 (7.9)***	−0.2 (7.3)
Ambulatory				
daytime (06.00–23.00 h)	127.5 (13.6)	−8.3 (7.8)***	−4.9 (8.0)*	−2.8 (7.0)
night (23.00–06.00 h)	109.8 (11.5)	−7.2 (6.0)***	−4.1 (8.5)	−7.2 (5.8)***
24 h mean	122.4 (12.5)	−8.0 (6.3)***	−4.7 (6.9)**	−4.1 (5.7)**
Diastolic pressure (mmHg)				
Casual	83.7 (9.1)	−5.5 (6.4)***	−6.3 (6.4)***	−1.2 (8.1)
Ambulatory				
daytime (06.00–23.00 h)	77.2 (8.2)	−4.4 (4.8)***	−1.9 (5.8)	−2.0 (5.8)
night (23.00–06.00 h)	62.4 (8.2)	−5.0 (6.2)**	−2.4 (6.9)	−5.3 (6.3)**
24 h mean	72.9 (7.9)	−4.6 (4.3)***	−2.1 (5.4)	−3.0 (5.0)*
Heart rate (beats/min)				
daytime (06.00–23.00 h)	83.5 (8.8)	−5.6 (8.4)**	−5.0 (9.4)*	−3.4 (6.1)*
night (23.00–06.00 h)	69.1 (8.7)	−7.1 (8.8)**	−4.4 (10.0)	−0.5 (9.4)
24 h mean	79.3 (8.0)	−6.1 (7.8)**	−4.9 (8.9)*	−2.6 (6.0)

Values are means (s.d.). * $P<0.05$, ** $P<0.01$, *** $P<0.001$ compared with baseline and using the rule of Bonferroni. In casual measurements, $n=29$ at baseline and on week 8, $n=28$ on week 17 and $n=27$ on week 52. In ambulatory measurements $n=25$ at baseline, on week 8 and 17 and on week 52, $n=22$.

Table 1 showed significant reduction during the VLCD, and returned to baseline levels thereafter. On long term follow-up, potassium excretion increased from baseline ($P<0.05$).

Correlations

Baseline. At baseline, 24 h mean ABPs did not correlate significantly with BMI ($r=0.34$ for systolic and $r=-0.04$ for diastolic), urinary sodium excretion, WHR, waist or age (data not shown). Serum insulin concentration correlated negatively with HDL cholesterol ($r=-0.38$, $P=0.05$) and positively with BMI ($r=0.39$, $P=0.04$). Initial lipid levels or glucose did not correlate with BMI (data not shown).

End of the treatment and one-year follow-up. At the end of the treatment, the changes in 24 h mean ABPs did not correlate significantly with changes in BMI ($r=0.17$ for systolic, $r=-0.13$ for diastolic) or urinary sodium excretion (data not shown). Change in cholesterol ($r=0.45$, $P=0.02$), HDL-cholesterol ($r=0.52$, $P=0.005$) and insulin ($r=0.37$, $P=0.05$) correlated with the change in BMI. Changes in glucose ($P=0.52$, $r=0.005$), triglyceride ($r=0.64$, $P<0.001$) and 24 h mean diastolic ABP ($r=0.51$, $P=0.01$) correlated with corresponding baseline levels.

At one-year follow-up, change in systolic 24 h mean ABP (from baseline) correlated with BMI change ($r=0.42$, $P=0.05$), but change in mean diastolic ABP did not correlate with BMI change ($r=0.2$). Change in insulin correlated with change in BMI ($r=0.40$, $P=0.04$). Change in glucose ($r=0.43$, $P=0.03$) and triglyceride ($r=0.55$, $P=0.003$) correlated with corresponding baseline levels.

In multivariate regression analyses initial risk factor levels, age, initial BMI and change in BMI were significant factors determining the changes in risk factors at the end of treatment and at one-year follow-up (Table 4). Urinary sodium excretion, fat distribution and their changes as independent variables in the model decreased the explanatory power of the model.

Discussion

In this 17-week weight loss programme with a VLCD, we report a significant weight reduction (16%) and concomitant decrease in several cardiovascular risk factors in moderately obese women. These short-term

Table 3 Fasting serum insulin, glucose and lipids at baseline and changes from baseline during and after weight loss programme

	Baseline (n=29)	*Week 8 (n=29)*	*Week 17 (n=28)*	*Week 52 (n=26)*
Insulin (mU/l)	10.4 (3.9)	−4.6 (3.1)***	−3.5 (3.7)***	−0.7 (3.8)
Glucose (mmol/l)	5.20 (0.56)	−0.61 (0.48)***	−0.22 (0.47)*	−0.28 (0.46)*
Triglyceride (mmol/l)	1.87 (0.95)	−0.74 (0.71)***	−0.55 (0.53)***	−0.35 (0.53)**
Cholesterol (mmol/l)	5.76 (1.27)	−1.05 (0.89)***	−0.35 (0.77)	+0.10 (0.81)
HDL-cholesterol (mmol/l)	1.19 (0.25)	−0.20 (0.20)***	+0.03 (0.19)	+0.16 (0.18)***

Values are means (s.d.). *$P<0.05$, **$P<0.01$, ***$P<0.001$ compared with baseline and using the rule of Bonferroni.

Table 4 Multivariate-regression analysis with change of the respective risk factor as dependent variable and initial risk-factor level, age, initial body mass index (BMI) and change of BMI as independent variables

Change of risk factor	*Initial risk factor level*	*Age*	*Initial BMI*	*BMI change*	*Multiple R2*
End of the treatment					
ABP systole	0.32 (0.12)*	0.22 (0.16)	−0.44 (0.50)	2.03 (1.03)	0.35
ABP diastole	0.39 (0.15)*	0.03 (0.13)	−0.55 (0.37)	0.67 (0.83)	0.36
Insulin	0.26 (0.21)	−0.04 (0.09)	0.13 (0.27)	0.99 (0.45)*	0.28
Glucose	0.44 (0.15)**	0.006 (0.01)	−0.01 (0.03)	0.04 (0.05)	0.31
Triglyceride	0.39 (0.09)***	0.0008 (0.009)	0.02 (0.03)	0.10 (0.05)	0.50
Cholesterol	0.17 (0.11)	0.004 (0.02)	0.02 (0.05)	0.24 (0.09)**	0.29
HDL-cholesterol	0.33 (0.12)**	0.004 (0.003)	0.02 (0.01)*	0.09 (0.02)***	0.50
One-year follow-up					
ABP systole	0.06 (0.10)	0.03 (0.16)	−0.71 (0.45)	0.72 (0.43)	0.29
ABP diastole	0.17 (0.12)	0.08 (0.13)	−0.87 (0.36)*	0.16 (0.35)	0.39
Insulin	0.68 (0.23)**	0.10 (0.08)	−0.21 (0.26)	0.87 (0.26)***	0.42
Glucose	0.34 (0.15)*	0.0005 (0.01)	−0.007 (0.03)	0.06 (0.03)	0.33
Triglyceride	0.37 (0.1)***	0.005 (0.01)	0.03 (0.03)	0.07 (0.03)*	0.45
Cholesterol	0.19 (0.12)	−0.04 (0.02)*	0.02 (0.05)	0.13 (0.05)**	0.31
HDL-cholesterol	0.27 (0.14)	−0.005 (0.004)	0.01 (0.01)	−0.01 (0.01)	0.24

Results are presented as regression coefficients (s.e.m.). *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$. ABP indicates 24 h mean ambulatory blood pressure.

results are in accordance with several earlier studies.[7,8,15,16]

Limited information is available for the maintenance of these improvements in risk factors during follow-up.[17] In our study, one-third of the weight lost was regained during the one-year follow-up, and improvements were sustained in serum triglycerides, glucose, waist circumference and night-time and 24 h ABPs. Total cholesterol increased to baseline level, but the sustained increase in HDL cholesterol reflects an overall positive change in lipids and has been reported by others.[15] The decrease in BP was smaller during weight maintenance than during energy restriction, which is consistent with previous studies.[18,19] Thus, despite some regain, this weight loss programme with VLCD seemed to be mainly efficient in controlling cardiovascular risk factors in middle aged women. The subjects with high initial risk factor levels and largest weight losses seemed to benefit most, but the power of this small study was probably too low to discover all factors that determined the changes in these risk factors.

Our study demonstrates the overall changes in risk factors during weight loss and follow-up. We cannot determine what impact behaviour changes, like increased physical activity, separate from weight loss, have on the cardiovascular risk factors during the programme and follow-up. In addition, changes in dietary pattern, like increased potassium intake at the follow-up visit, may have had an additional favourable effect on BP.

In this study, the ABP fell significantly during the VLCD (24 h mean −8.0/−4.6 mmHg), but during further weight loss with less severe energy restriction, the ABP decrease seemed to diminish. After VLCD, sodium excretion increased to baseline level. Controversial results have been reported for the effect of sodium restriction on BP during weight loss.[9] Our result is in accordance with some previous studies, which have shown that unrestricted sodium intake can partly offset the hypotensive response to weight loss.[18,19] However, the importance of sodium restriction during energy restriction has been questioned by others,[20] especially during weight loss with a VLCD.[7,21]

Weight loss studies have seldom reported 24 h ABP monitoring results. Thus, it is not possible to compare our results directly with earlier studies. Our study showed that a sustained mean weight loss of 10.7 kg can produce an average reduction in 24 h ABPs of 4.1/3.0 mmHg in middle-aged obese women with normal or high normal BP. This study is limited in the respect that it did not have a no-intervention control group. Therefore regression to the mean may partly explain BP decreases. Compared to conventional BP measurements, however, ABP monitoring has been shown to be largely, but not entirely, without BP lowering effect associated with time.[22]

The night-time ABPs remained significantly below the baseline (−7.2/−5.2 mmHg) at the one-year follow-up, but not at the end of the treatment period. We do not know the reason for this long-term night-time response. One possibility is that weight loss may have resolved sleep disturbances in some subjects and thus resulted in the BP decrease at night. A decrease in sympathetic nervous activity after weigh loss may be another factor. In the present study, sleeping hours and quality of sleep were not checked from patient diaries. The monitoring was undertaken in different seasons: baseline and one-year monitoring in winter and end-treatment in summer—this may be one factor affecting the results.

Using a cuff bladder which is not an appropriate width for the arm circumference may cause errors in BP measurement, but this can be corrected with the table provided by Maxwell *et al*.[23] In weight loss studies of obese subjects, the cuff size is often overlooked and it may cause discrepancies in BP results.

We used appropriate cuff bladders during this study to overcome the problem.

Conclusion

We have demonstrated several beneficial changes in cardiovascular risk factors in moderately obese normo- and mildly hypertensive women, during and after weight loss. Despite partial weight regain, these changes were mostly maintained at the one-year check-up. Sodium intake tended to increase during the follow-up year. To avoid this, weight loss programmes should also contain some information on reduction of excess dietary salt.

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