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ORIGINAL ARTICLE

Metabolic sequelae of β-blocker therapy: weighing in on the obesity epidemic?

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Background: Sympathetic activation is an important metabolic adaptation limiting weight gain. Propensity of weight gain associated with β-blocker therapy in the obese modern population is unknown.
Objective: To determine whether chronic β-blocker therapy reduces energy expenditure (EE) and increases body weight.
Methods: We undertook (i) a mechanistic study comparing EE, diet-induced thermogenesis and habitual activity between healthy volunteers ($n=11$) with uncomplicated hypertension treated with a β-blocker and anthropometrically matched controls ($n=19$) and (ii) three cross-sectional studies comparing body weight, body mass index (BMI) and waist circumference between β-blocker treated and untreated patients from ambulatory patients attending (a) diabetes outpatient clinic ($n=214$), (b) hypertension outpatient ($n=84$) and (c) participants in a multi-centre type 2 diabetes trial (ADVANCE) ($n=11140$).
Results: Among weight-matched β-blocker users, diet-induced thermogenesis, fat oxidation rate and weekly habitual activity were lower by 50% ($P<0.01$), 32% ($P=0.04$) and 30% ($P<0.01$), respectively, compared with controls. In β-blocker treated patients, the adjusted mean body weight was 9.2 ± 1.2 kg ($P=0.0002$) higher among those attending the diabetes clinic, 17.2 ± 3.2 kg ($P=0.004$) higher among those attending the hypertension clinic and 5.2 ± 0.7 kg ($P=0.0003$) higher at baseline among participants in the ADVANCE trial compared with patients not treated with β-blockers. BMI displayed a similar difference.
Conclusions: EE is reduced and body weight increased in chronic β-blocker users. We hypothesise that chronic β-blockade causes obesity by blunting EE.
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Keywords: β-blocker; energy expenditure; diet-induced thermogenesis; brown adipose tissue; habitual activity

Introduction

Obesity is epidemic worldwide and is associated with significant morbidity and mortality.[1,2] More than two-thirds of men and half of women over the age of 25 years in the United States are overweight or obese according to the National Health and Nutrition Examination Survey III.[3] The prevalence of obesity in the United Kingdom nearly doubled in the last decade in men and rose by more than 50% in women.[4] The causes of obesity are multi-factorial with nutritional, lifestyle and genetic causes being the most widely researched. The possibility that medication use may contribute to obesity has received little attention.

The sympathetic nervous system stimulates energy expenditure (EE) and fat utilisation.[5] Bray and others have hypothesised a causative relationship between low sympathetic drive and development of obesity.[6–9] The importance of the sympathetic nervous system in the regulation of energy homeostasis is shown by animal studies, demonstrating that obesity develops from a reduction in EE induced by ablation of adrenergic receptors.[10] In humans, β-blocker *acutely* blunts EE, substrate utilisation and aerobic exercise capacity.[11–15] However, chronic adrenergic inhibition results in β-adrenoceptor upregulation in animals, indicating possible loss of efficacy.[16] The extent to which chronic β-blocker therapy impairs EE and physical activity in otherwise healthy individuals has not been investigated. β-blockers are commonly prescribed to patients for hypertension, which

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frequently occurs with many other co-morbidities. The level of physical activity among patients with chronic co-morbidities, who as a group tend to be sedentary, may be further restricted. Thus, there is a strong possibility that medications, which chronically blunt sympathetic nervous system activity may predispose to obesity.

The aim of these studies was to investigate whether long-term therapy with a β-blocker impairs EE and habitual activity and increases adiposity.

Subjects and methods

We undertook a mechanistic study of energy metabolism and an anthropometric evaluation of adiposity in three separate population groups: Study 1, mechanistic study, and Study 2, anthropometric study. Group a: patients attending the Diabetes Clinic, St Vincent's Hospital. Group b: patients attending the Hypertension Clinic, St Vincent's Hospital. Group c: community dwelling individuals who participated in an evaluation of the effects of blood pressure lowering and glucose control on vascular outcomes in patients with type 2 diabetes—*The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial*.[17] The Human Research Ethics Committee, St Vincent's Hospital, approved the studies.

Subjects, study design and clinical protocol

Study 1: mechanistic study. We compared EE between β-blocker treated individuals and volunteers treated with anti-hypertensive medications other than β-blocker, matched for age, gender and body mass index (BMI). Those on β-blockers had been treated for 9 ± 2 years. The dose of β-blocker is expressed as the defined daily dose to facilitate comparison. The defined daily doses reflect the assumed daily dose of a medicine when used for its main indication by adults.[18] Three aspects of EE, namely resting EE, diet-induced thermogenesis and physical activity, were assessed. Subjects were recruited from the general public through local advertisements. The indication for β-blocker therapy was hypertension in every case. Participants were in otherwise good health, all leading independent lives and not functionally restricted. Individuals were excluded if they had significant organ dysfunction, were receiving medications that potentially altered metabolism, were receiving glucocorticoids, had diabetes, had an active infection, congestive heart failure, hepatic or renal disease or a malignancy.

Resting EE and diet-induced thermogenesis were assessed by indirect calorimetry after an overnight fast, as previously described.[19] EE and rate of fat oxidation were calculated by the equations laid out by Frayn[20] and Ferrannini.[21] The mean day-to-day intrasubject coefficient of variation for EE at our Institute is about 4%.[22,23] The postprandial incremental area under the curve was calculated by the trapezoidal method, inclusive of the basal period, by subtracting baseline values extrapolated over 120 min from the total postprandial area. Diet-induced thermogenesis was estimated by recording the increase in EE at 120 min after a standardised meal (ensure plus: 14.8% protein, 57% carbohydrate and 28.2% fat), expressed as a percentage of baseline.

Assessment of body composition. Dual-energy X-ray absorptiometry using a total body scanner (Lunar model DPX, software version 3.1; Lunar Corp., Madison, WI, USA) was used to measure fat mass and lean body mass. Amount of central abdominal fat contained within a manually traced region was estimated, as previously described.[24] At our institution, the coefficient of variation for fat mass and lean body mass are 2.9 and 1.4%, respectively.[23]

Estimation of physical activity. Habitual activity was assessed over a duration of 1 week by i) quantifying pedometry steps (Digi-Walker electronic pedometer, Yamax Co., Yasama Corp., Tokyo, Japan) and ii) using a 7-day activity recall questionnaire.[25]

The Yamax pedometre is worn above the right or left hip and clipped to the waistband using an integral belt clip. Subjects wore the pedometer at all wake hours, except when swimming and showering. As recording may possibly alter the behaviour of participants, each pedometer was taped such that the participants were blinded to the recording of their steps. The variability and reliability of the Yamax pedometer used in the study were initially determined in accordance with previous recommendations.[26] Five pedometers were tested at our institution before use in the research study. Four volunteers wore the pedometers for 2 weeks and weekly pedometry steps were recorded at the end of each week. The mean week-to-week intrasubject coefficient of variation for pedometry steps was 4.2%. To investigate whether the pedometer registers readings during motorised travel, two subjects wore their pedometers on two separate occasions during a car and a train trip. The pedometer does not detect movement changes during locomotor travel.

The 7-day activity recall questionnaire is designed specifically for mature subjects, assessing participation in household chores and leisure activities. Participants were asked to recall morning, afternoon and evening activities for the previous day until a full 7 days of information on minutes spent engaged in vigorous-intensity and moderate-intensity activities and sleep had been obtained. Cues are used to prompt classifications of activity into their respective intensities. To calculate EE in terms of metabolic equivalents (MET), the estimated time at different intensities of physical activity is multiplied by the participant's body weight. Direct questions consider the time (minutes per day) spent at moderate (4 MET), hard (6 MET), or very hard (10 MET) physical activities, and time (hours per day) spent asleep (1 MET). Light (1–4 MET) physical activity is determined by

subtracting hours sleeping and hours of moderate, hard and very hard physical activities from the total hours in a week.

Study 2: anthropometric study. A cross-sectional evaluation of adiposity data stratified according to β-blocker use was undertaken in consecutive patients attending (a) the diabetes clinic between January 2007 and January 2008 and (b) the hypertension clinic between February and April 2008, at St Vincent's Hospital, Sydney, Australia. For the patients from the diabetes clinic, patients with type 1 or secondary diabetes mellitus, cardiac failure, severe renal or hepatic impairment and patients taking corticosteroids were excluded. For patients from the hypertension clinic, the same exclusion criteria were applied with the additional exclusion of all patients with known diabetes mellitus.

Patient characteristics, including age, sex, past medical history and current medications, were recorded. Body weight and height were measured on the same electronic scale. BMI was calculated as body weight in kilograms divided by the square of height in metres. Waist circumference was measured using a flexible tape placed on a horizontal plane at the level of the iliac crest as seen from the anterior view by the same clinician (PL). Duration of β-blocker use was determined by reviewing medical records of individual users for documentation of commencement dates; in cases when commencement date was not recorded (for example, when β-blocker therapy was initiated by other health professionals), the date of the medical consultation when β-blocker was first recorded in the medication list was considered as the date of commencement.

Group c includes participants of the ADVANCE trial. ADVANCE was a randomised factorial trial designed to investigate the effects of routine blood pressure lowering and intensive glucose control on vascular outcomes in patients with type 2 diabetes.[17] The main results have been reported previously.[27] We undertook an evaluation of adiposity in this large cohort stratified by β-blocker usage at entry and completion of the study. Anthropometric parameters and medication history were collected at entry to the study as previously described.[27] Body weight, calculated BMI and waist circumference were compared between β-blocker users and non-users.

Statistical methods

Statistical analysis was undertaken using the statistical software package SPSS 17.0 (SPSS, Inc., Chicago, IL, USA). Data are expressed as mean ± standard error of the mean for normally distributed continuous variables. Statistical differences between groups were assessed using unpaired *t*-tests. Differences between categorical variables were assessed using the χ^2-test.

In Study 2, multivariate linear regression models using analysis of variance were constructed to explore the role of potential confounders to BMI including age, gender, use of oral hypoglycaemic medications and other anti-hypertensive medications, glycaemic control (HbA1c), blood pressure, renal function and ischaemic heart disease. $P<0.05$ was considered statistically significant.

Results

Study 1: mechanistic study

The 11 chronic β-blocker users (7 women, 54–78 years old) and 19 controls recruited were well matched for age, BMI and adiposity, as shown in Table 1. These subjects were treated with atenolol or metoprolol, selective β_1-blockers, at a mean dose of 0.67 ± 0.10 defined daily doses. Eight controls were on an aldosterone receptor blocker, seven on an angiotensin converting enzyme inhibitor and four on calcium channel blocker. Heart rate was significantly lower ($P<0.02$) in β-blocker users than in controls, whereas mean blood pressure was not significantly different.

Energy expenditure and substrate utilisation. Resting EE was not different between β-blocker and control groups (1484 ± 54 vs 1309 ± 74 kcal per day, P = NS). Mean basal fat oxidation rate was 32% lower (37.5 ± 4.7 vs 49.5 ± 6.2 mg min^{-1}, $P=0.04$) in the β-blocker group (Figure 1a). EE was enhanced 120 min after the meal by 8.7 ± 4.4 and 15.5 ± 3.2%. Diet-induced thermogenesis in β-blocker users was significantly blunted ($P<0.01$), ~50% of that in the control group (Figure 1b). Fat oxidation tended to be suppressed to a greater extent after the meal among β-blocker users (−57 ± 42 vs −15 ± 12%, $P=0.2$).

Habitual activity. The mean weekly cumulative step count was significantly less (38816 ± 7699 vs 58944 ± 7330, $P<0.01$) (Figure 1c), ~30% lower than that of the control group. Quantification of total EE in METs using a 7-day activity-recall questionnaire showed a weekly level that was

Table 1 Comparison of healthy volunteers with uncomplicated hypertension treated with long-term β-blocker and age-, gender- and anthropometrically-matched controls from mechanistic study (Study 1)

	β-blocker users	*Controls*	P
N	11	19	
Female	7	12	
Age (years)	69 ± 1	68 ± 2	NS
Height (cm)	168 ± 1	166 ± 1	NS
Body weight (kg)	80.4 ± 0.3	76.5 ± 3.3	NS
BMI (kg m^{-2})	28.4 ± 0.7	27.4 ± 0.9	NS
Pulse rate (beats per min)	60 ± 1	72 ± 2	0.02
SBP (mm Hg)	147 ± 1	144 ± 1	NS
DBP (mm Hg)	84 ± 1	84 ± 1	NS
Percentage of fat mass	40.9 ± 1.0	39.6 ± 1.5	NS
Percentage of lean mass	57.2 ± 1.0	58.5 ± 1.6	NS
Lean : fat mass	1.6 ± 0.7	1.8 ± 0.3	NS
Percentage of central fat mass	40.7 ± 1.0	38.9 ± 1.4	NS

Abbreviations: DBP, diastolic blood pressure; NS, non-significant; SBP, systolic blood pressure. Data are expressed as mean ± s.e.

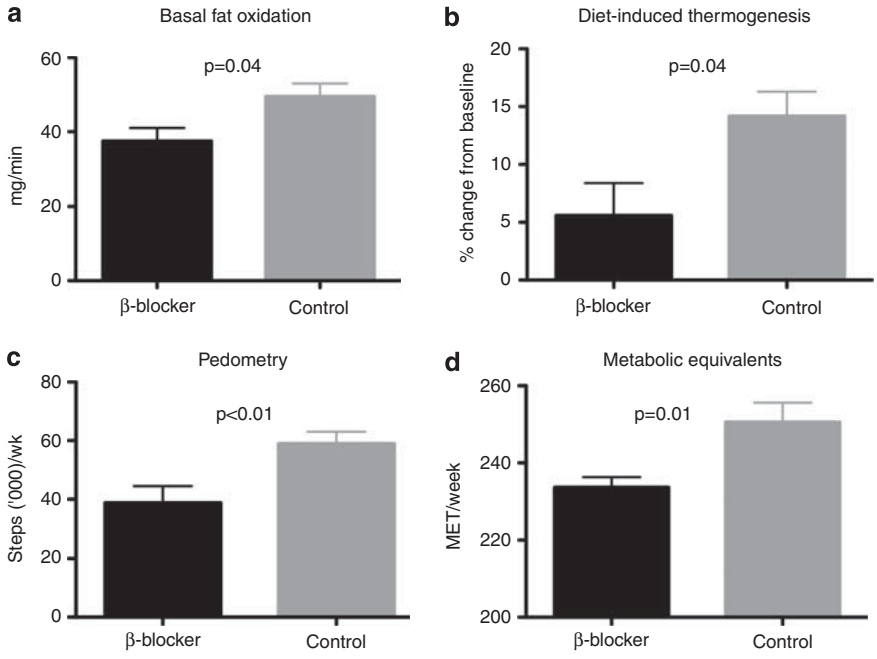

Figure 1 Comparison of fat oxidation, diet-induced thermogenesis and physical activity between healthy volunteers with uncomplicated hypertension treated with long-term β-blocker (black) and age-, gender-, and anthropometrically matched controls (grey) (Study 1: mechanistic study).

~10% lower (Figure 1d), in the β-blocker group ($P=0.01$). The β-blocker treated individuals spent on average 98 ± 1% of waking hours in light activities, compared with 93 ± 1% amongst controls ($P=0.02$).

Study 2: anthropometric study: diabetes clinic

Among a total of 214 consecutive patients attending the diabetes clinic, 30% ($n=64$) were taking β-blockers. The duration of β–blocker use was >3 years in all patients, with an estimated mean duration of 7 years (3.2–21.5 years). Mean body weight was significantly higher ($P=0.002$) in β-blocker users (Table 2), who were 9.2 ± 5.7 kg heavier than non-users. Similarly, BMI was significantly higher in β-blocker users by 3.6 ± 6.3 kg m^{-2} ($P=0.0002$) (Figure 2).

More than 50% of β-blocker users were treated with >2 anti-hypertensive medications, a proportion twice that observed among non-users ($P<0.01$). Significantly more β–blocker users were also treated with diuretics, calcium channel blockers and α-blockers (Table 2). Comparison of BMI between users and non-users of other anti-hypertensive and diabetes medication showed that those treated with metformin, diuretics, angiotensin receptor blockers and calcium channel blockers to be significantly heavier (Table 3). In summary, the more obese patient had a greater likelihood of being treated with β-blockers as well as other anti-hypertensive and diabetes medications.

We next examined whether BMI was different between patients on polytherapy (⩾2 anti-hypertensive medications) and those on monotherapy. Among patients not treated with β-blockers, BMI of the polytherapy subgroup was higher (33.5 ± 6.3 kg m^{-2} vs 29.5 ± 6.4 kg m^{-2}, $P=0.003$) than in the monotherapy subgroup. However, among β-blocker users, the mean BMI was not different significantly between the polytherapy and monotherapy (treated with β-blocker alone) subgroups. In summary, obesity was linked to a greater prescriptive use of anti-hypertensive medications. However, obesity observed among β-blocker users was independent of other anti-hypertensive medication use.

A step-wise multiple regression, including age, gender, HbA1c, history of hypertension, blood pressure, current smoking, history of macrovascular diseases, and use of insulin, metformin, sulphonylureas, thiazolidediones, angiotensin-converting enzyme inhibitors, antiogensin II receptor blockers, calcium channel blockers, diuretics and α-blockers as independent variables, demonstrated that β-blocker use, together with metformin and diuretic use, age, female gender and HbA1c, were independently associated with higher BMI (adjusted $R^2=0.21$, $P<0.0001$). The order of effect was β-blocker ($R^2=0.064$), metformin ($R^2=0.051$), age ($R^2=0.032$), diuretics ($R^2=0.023$), HbA1c ($R^2=0.021$) and female gender ($R^2=0.017$).

Study 2, anthropometric study: hypertension clinic

Among 84 consecutive patients recruited, 50% ($N=42$) were treated with β-blockers for at least 3 years, with an estimated mean duration of therapy of 12 years (3.7–27 years). Mean body weight, BMI and waist circumference were significantly higher in the β-blocker group (Table 2 and Figure 2).

Table 2 Comparison of β-blocker users and non-users in the diabetes clinic and hypertension clinic

	Diabetes clinic			*Hypertension clinic*		
	β-blocker users	*Non users*	P	*β-blocker users*	*Non users*	P
N	64	150	—	42	42	—
Female (%)	36	43	NS	8	9	NS
Age (years)	68 ± 12	67 ± 1	NS	72 ± 2	70 ± 2	NS
Systolic blood pressure (mm Hg)	134 ± 3	135 ± 2	NS	134 ± 2	133 ± 3	NS
Diastolic blood pressure (mm Hg)	72 ± 2	73 ± 1	NS	75 ± 1	73 ± 1	NS
Body weight (kg)	92.0 ± 3	83.1 ± 1.7	0.002	89.3 ± 3.0	72.1 ± 2.1	0.01
Height (cm)	165 ± 2	165 ± 1	NS	165 ± 1	166 ± 1	NS
Waist circumference (cm)	NA	NA	NA	109 ± 2	89 ± 2	0.0001
Percentage of patients using:						
Insulin	42	27	NS	—	—	—
Metformin	66	68	NS	—	—	—
Sulphonylureas	47	46	NS	—	—	—
Thiazolidindiones	6	5	NS	—	—	—
Angiotensin-converting enzyme inhibitors	41	32	NS	38	33	NS
Angiotensin II receptor blockers	41	29	NS	24	38	NS
Diuretics	44	18	0.0006	57	29	0.05
Calcium-channel blockers	38	21	0.03	62	52	NS
α-blockers	8	1	0.004	24	10	NS
Percentage of patients with history of:						
Ischaemic heart disease	36	15	0.002	38	14	0.03
Stroke	16	8	NS	5	0	NS

Abbreviations: NA, not available; NS, non-significant. Data are expressed as mean ± s.e.

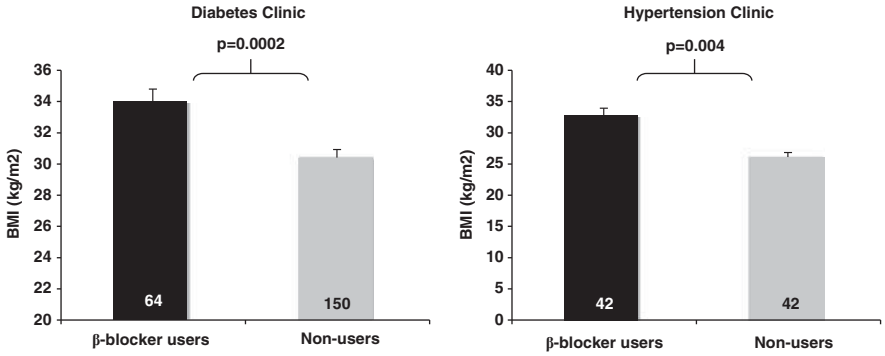

Figure 2 Comparison of BMI between β-blocker users and non-users from diabetes clinic and hypertension clinic.

Table 3 Differences in BMI of patients attending the diabetes clinic and hypertension clinic on different medications

	Diabetes clinic				*Hypertension clinic*			
	%	*Users*	*Non users*	P	*%*	*Users*	*Non users*	P
Insulin	31	30.8 ± 0.8	31.9 ± 0.6	NS	—	—	—	—
Metformin	70	32.6 ± 0.5	29.2 ± 0.8	0.0005	—	—	—	—
Sulphonylureas	47	31.8 ± 0.7	31.3 ± 0.6	NS	—	—	—	—
Thiazolidindiones	5	31.6 ± 0.5	31.7 ± 1.8	NS	—	—	—	—
Angiotensin-converting enzyme inhibitors	35	31.6 ± 0.7	31.5 ± 0.6	NS	36	28.2 ± 0.9	30.2 ± 1.0	NS
Angiotensin II receptor blockers	33	33.5 ± 0.9	30.6 ± 0.5	0.002	31	29.7 ± 1.1	29.4 ± 1.0	NS
Diuretics	26	34.1 ± 1.0	30.6 ± 0.5	0.0008	44	30.9 ± 1.3	28.4 ± 0.9	NS
Calcium-channel blockers	27	33.3 ± 0.8	30.9 ± 0.6	0.02	57	30.2 ± 0.9	28.5 ± 1.3	NS
α-blockers	3	31.5 ± 0.5	32.6 ± 2.0	NS	17	29.4 ± 1.6	29.5 ± 0.9	NS

Abbreviations: BMI, body mass index; NS, non-significant. '%' represents percentage of patients on particular medication. Data are expressed as mean ± s.e.

Applying the waist circumference criteria of the National Cholesterol Education Programme for the metabolic syndrome (>102 cm in men and >88 cm in women),[28] the prevalence of central obesity was more than twofold higher in the β-blocker group (55 vs 21%, $P<0.001$).

Among patients from the hypertension clinic, β-blocker users were also more likely to be co-treated with multiple anti-hypertensive medications. Ninety-eight per cent of β-blocker users were receiving poly-therapy, as compared with only 50% of non-β-blocker users receiving poly-therapy ($P<0.01$). We next determined whether BMI was different between patients on polytherapy and monotherapy. Amongst patients receiving poly-therapy, both BMI and waist circumference were higher in β-blocker users than non-users ($32.9\pm7.2\,kg\,m^{-2}$ vs $25.8\pm4.0\,kg\,m^{-2}$, $P=0.0003$ and 109 ± 14 cm vs 90 ± 11 cm, $P=0.0001$). However, BMI was not greater among users of anti-hypertensive medications other than β-blockers, compared with non-users (Table 2). Thus, among patients from the hypertension clinic, only patients treated with β-blockers and not other anti-hypertensive medications were heavier.

A step-wise multiple regression, including age, gender, current smoking, blood pressure, history of macrovascular diseases, renal function and use of angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, calcium channel blockers, diuretics and α-blockers as independent variables, demonstrated that β-blocker use and a higher calculated glomerular filtration rate were independently associated with higher BMI (adjusted $R^2=0.27$, $P<0.0001$). The order of effect was β-blocker ($R^2=0.23$) and GFR ($R^2=0.04$).

Study 3, anthropometric study: ADVANCE trial

Among 11 140 patients enrolled in the trial, 24% ($N=2728$) were treated with β-blockers (Table 4). Significantly more β-blocker users were also treated with sulphonylureas, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, diuretics and calcium channel blockers (Table 4).

Mean body weight, BMI and waist circumference were significantly ($P<0.001$) higher in the β-blocker group by 5.2 ± 0.7 kg, $1.7\pm0.2\,kg\,m^{-2}$ and 4.0 ± 0.5 cm (Figure 3). Patients treated with metformin, thiazolidindiones, diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and calcium channel blockers were significantly heavier than subjects not receiving these medications (Table 5). Differences in BMI ($P=0.0003$) and waist circumference ($P=0.04$) between β-blocker treated and non-treated patients remained significant after adjustment for age, sex, history of macro-vascular disease, current smoking, history of hypertension, blood pressure, anti-hypertensive medications, diabetes medications and HbA1c.

Body weight did not change in either β-blocker treated or un-treated participants (0.37 ± 0.13 vs 0.24 ± 0.07 kg, $P=$NS) over the 5-year period and β-blocker treated participants remained 6% heavier than non-treated participants (81.5 ± 0.3 vs 76.5 ± 0.2 kg, $P<0.001$).

Table 4 Comparison of β-blocker users and non-users from ADVANCE

	β-blocker users	*Non users*	P
N	2728	8409	—
Female (%)	1122 (41)	3610 (43)	0.09
Age (years)	65.5 ± 0.1	65.8 ± 0.1	0.03
Systolic blood pressure (mm Hg)	147 ± 0.4	144 ± 0.2	<0.0001
Diastolic blood pressure (mm Hg)	82 ± 0.2	80 ± 0.1	<0.001
Body weight (kg)	81.9 ± 0.3	76.8 ± 0.2	<0.001
Macrovascular disease (%)	1357 (50)	2233 (27)	<0.0001
Medication use (percentage of patients)			
Insulin	1	1	NS
Metformin	59	61	0.052
Sulphonylureas	68	72	<0.001
Thiazolidindiones	3	4	NS
Angiotensin-converting enzyme inhibitors	56	39	<0.001
Angiotensin II receptor blockers	6	5	0.02
Diuretics	35	20	<0.0001
Calcium-channel blockers	37	29	<0.0001

Abbreviation: NS, non-significant. Data are expressed as mean ± s.e.

Discussion

This study investigated the metabolic and body weight sequaelae of chronic β-blocker therapy. Among volunteers matched for gender, age and BMI, EE and the rate of fat utilisation were lower among those treated with β-blockers. The β-blocker users are less active physically even when they are weight matched. Body weight and BMI were consistently higher among β-blocker treated patients attending the diabetes and hypertension Clinics and among community dwelling patients with diabetes participating in a multi-centre international trial. Our studies across four populations indicated those treated chronically with β-blockers are consistently more obese with significant blunting of diet-induced thermogenesis, fat utilisation and habitual activity.

Our mechanistic study is the first to determine whether long-term β-blocker treatment affects EE, fat utilisation and habitual activity in otherwise healthy individuals. As body weight and composition influence resting EE, substrate utilisation and physical fitness, we performed the evaluation by careful matching of body weight and composition. We found a 50% suppression of diet-induced thermogenesis and 32% reduction in fat oxidation. When matched for weight, the level of habitual activity, as estimated by pedometry and by MET quantification was up to 30% lower among β-blocker chronic recipients in good health. These changes will predispose to a gain in fat mass in the face of unaltered nutritional intake. Indeed our body weight studies reveal BMI to be consistently higher across three different populations of patients with diabetes and/or hypertension on chronic β-blocker therapy.

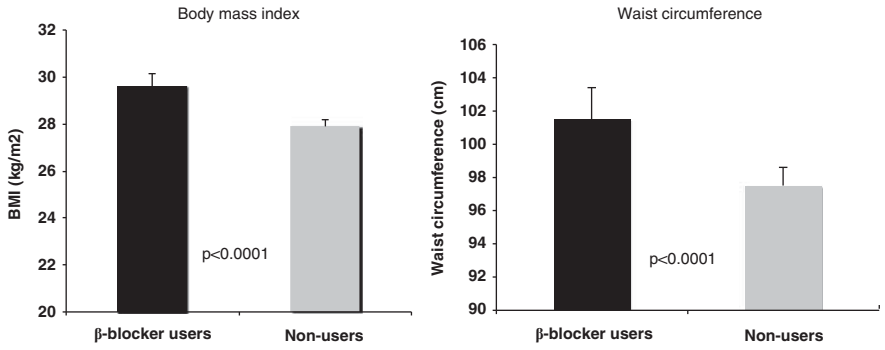

Figure 3 Comparison of baseline BMI and waist circumference between β-blocker users and non-users from ADVANCE.

Table 5 Differences in BMI for ADVANCE participants on different medications

	%	*Users*	*Non users*	P
Insulin	1.4	28.2+0.4	28.3+0.1	0.76
Metformin	60.6	28.6+0.1	27.8+0.1	<0.0001
Sulphonylureas	70.9	27.9+0.1	29.2+0.1	<0.0001
Thiazolidindiones	3.6	30.0+0.3	28.2+0.1	<0.0001
Angiotensin-converting enzyme inhibitors	43	29.3+0.1	27.5+0.1	<0.0001
Angiotensin II receptor blockers	5.5	29.8+0.2	28.2+0.1	<0.0001
Diuretics	23.7	30.3+0.1	27.7+0.1	<0.0001
Calcium-channel blockers	30.8	28.7+0.1	28.1+0.1	<0.0001
Other anti-hypertensive medications	12.4	28.4+0.1	28.3+0.1	0.46

Abbreviation: BMI, body mass index. '%' represents percentage of patients on particular medication. Data are expressed as mean ± s.e.

There is strong evidence from rodent studies that brown adipose tissue (BAT) contributes significantly to diet-induced thermogenesis.[29] Deletion of β-adrenoceptors in mice result in diminished BAT mass and abrogation of DIT, indicating that BAT mediates a major component of DIT.[10] Until recently, it was believed that BAT did not exist in adult humans, however, advances in positron-emission tomography-CT have provided strong evidence that BAT persists in adult life as reflected in the avid uptake of glucose tracer into fat in up to 64% of adults.[30] The observation that uptake of glucose tracer is abrogated by β-blockers suggests that the blunting of DIT observed in our study may occur in part from a reduction in BAT activity.[31]

The cross-sectional observational design on adiposity is a weakness of the current study. Despite careful adjustment for potential confounders, a causal relationship between β-blocker use and weight difference cannot be established with certainty. It is possible that the association between β-blocker use and greater weight is confounded by a greater prescriptive use of anti-hypertensive agents to patients who are more obese. However, we did not find evidence for this among patients from the hypertension clinic (Table 2). In addition, analysis revealed that differences in anthropometric measures attributable to β-blocker use remained significant after adjusting for the concurrent use of other anti-hypertensive medications. The observation that BMI among β-blocker users with diabetes was not different between those receiving polytherapy and monotherapy, suggests polytherapy itself was not associated with higher BMI. These findings support an independent association of β-blocker with obesity. The striking consistency in weight difference observed between β-blocker treated and non-treated patients in three different settings provide strong evidence for an obesogenic effect of β-blocker therapy, as supported by mechanistic evidence from evaluation of EE.

Two systematic reviews of 10 prospective, randomised, controlled trials of the anti-hypertensive efficacy of β-blockers have reported that β-blockers increases body weight.[32,33] However we have observed a greater weight difference between β-blocker users and non-users than those previously reported.[32,33] β-blocker use was associated with weight gain of up to 3.4 kg compared with those taking anti-hypertensive medications other than β-blockers.[34–41] In our anthropometric study, we observed an apparent greater effect, with a mean weight difference of 5–17 kg between β-blocker users and non-user. It is not possible to deduce the extent to which selection bias and reverse causality added to the effect of β-blocker on body weight we observed. The mean BMI ($\sim 31\,kg\,m^{-2}$) of patients from our outpatient clinics was 6–15% higher than subjects in the early studies,[34–37,41] equating ~5–12 kg heavier (for a person 1.8 m tall). The greater mean weight difference raises the possibility that their effects may be amplified in a more obese contemporary population that is characterised by unhealthy diets and sedentary behaviours. Indeed, caloric intake in the average adult has increased by up to 20% between 1971–2000 and physical activity has declined substantially,[42,43] resulting in doubling of the prevalence of obesity in the last two decades in the United States, United Kingdom and Australia.[3,4,44,45]

As our mechanistic study reveals significant blunting of DIT and habitual activity among chronic β-blocker, we hypothesise the exaggeration of these metabolic defects in an increasingly sedentary and nutrition toxic modern environment may contribute to the greater weight difference observed in our studies. Previous studies have generally

neglected the impact of β-blocker on habitual activity. Weekly pedometry steps were ~21 000 less among β-blocker treated individuals compared with controls. With the assumption of a caloric cost of 60 kcal per km for an individual weighing 70 kg,[46] the difference in pedometry steps per week would account for a difference in ~950 kcal per week and 50 000 kcal per year. This energy deficit is equivalent to 5.3 kg of fat, assuming 1 g fat contains 9.3 kcal energy. Thus in face of an unaltered energy intake, the reduction in habitual activity alone would account for significant weight gain in the long term. Although metabolic studies were not performed during exercise, it is likely that β-blocker induced reduction in exercise capacity, diminishing overall EE and lipid mobilisation may accentuate weight gain in our patients.[47,48]

The dynamics of weight gain caused by β-blocker has been examined by Sharma *et al*.[32] Based on weight regression analysis, they concluded that weight gain occurred predominantly in the first few months of β-blocker use.[32,34–38,40,41,49,50] Although we found a lack of progression in weight difference between the β-blocker treated and non-treated participants of the ADVANCE study, β-blocker users failed to lose weight and β-blocker treated participants remained 6% heavier than non-treated participants. The reasons for the maintenance of a higher weight during β-blocker therapy is unclear but may be secondary to metabolic maladaptations and establishment of a new weight 'set-point'.[32,51]

The impact of an obesogenic medication on the prevalence of obesity on a population level depends on the extent of prescriptive use. We obtained national prescription data of β-blockers in Australia. The β-blocker atenolol was the seventh most commonly prescribed drug in 2005. There were 66 705 917 β-blocker prescriptions recorded between 1996–2006, representing a 44% increase over the 10-year period (unpublished data). The prevalence of obesity has doubled between 1980 and 2002 in Australia and elsewhere.[3,44] We hypothesise that the high prevalence of β-blocker usage may be contributing to the escalation of obesity in the community.

In summary, the current study reveals that chronic β-blocker users are more obese. They exhibit reduced levels of diet-induced thermogenesis, fat utilisation and physical activity, changes that lead to the development of obesity. In view of the high and increasing prevalence of β-blocker usage nationally, it is our hypothesis that pharmacological blockade of sympathetic nervous system function in therapeutic doses for hypertension could contribute to the burden of obesity in modern day, more obese society.

Conflict of interest

Dr John Chalmers has received research grants for the ADVANCE trial from Servier International, administered through the University of Sydney. Dr Paul Lee was funded by an Australian National Health Medical Research Council postgraduate scholarship. Dr Kengne, Dr Greenfield, Dr Day and Dr Ho declare no conflict of interest.

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