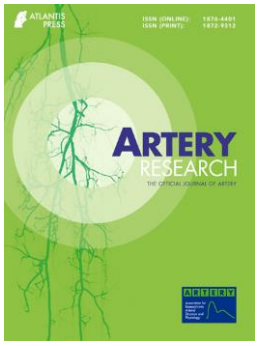

Artery Research

ISSN (Online): 1876-4401 **ISSN (Print): 1872-9312**
Journal Home Page: https://www.atlantis-press.com/journals/artres

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To cite this article: A. Chakera, S. Bunce, C. Heppenstall, J.C. Smith (2010) The effects of weight loss using dietary manipulation and rimonabant therapy on arterial stiffness in type 2 diabetes, Artery Research 4:2, 47–51, DOI: https://doi.org/10.1016/j.artres.2010.04.001

To link to this article: https://doi.org/10.1016/j.artres.2010.04.001

Published online: 21 December 2019

Artery Research (2010) 4, 47–51

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/artres

The effects of weight loss using dietary manipulation and rimonabant therapy on arterial stiffness in type 2 diabetes

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Received 4 January 2010; received in revised form 26 March 2010; accepted 8 April 2010

KEYWORDS
Diabetes;
Arterial stiffness;
Obesity

Abstract *Background:* Obesity is considered an important factor contributing to premature arterial stiffening in type 2 diabetes but it is uncertain whether weight loss through dietary modification leads to a reduction in arterial stiffness. Rimonabant is an anti-obesity drug which, through its pharmacological action of cannabinoid receptor blockade, could exert effects on central haemodynamics.
Methods: In an open design, 29 obese subjects with type 2 diabetes were studied. Subjects were studied before, during and after 6 months dietary intervention with (20 subjects), or without (9 subjects) rimonabant. Arterial stiffness (aortic and brachial pulse wave velocity), central aortic pressure and wave reflection were assessed non-invasively (Sphygmocor).
Results: After 6 months (in comparison with baseline), there were reductions in weight (104 ± 21 versus 107 ± 21 Kg, $p < 0.001$), and improvements in HbA1c (7.3 ± 1.4 at 3 months, $p < 0.01$ and 7.4 ± 1.5 at 6 months, $p = 0.06$ versus $7.7 \pm 1.5\%$ at baseline) and HDL cholesterol (1.3 ± 0.2 versus 1.2 ± 0.3 mmol/L, $p < 0.001$). Aortic diastolic pressure (82 ± 10 versus 85 ± 8 mmHg, $p < 0.05$) was lowered despite unchanged peripheral mean arterial pressure. No reductions in aortic stiffness or wave reflection were observed.
Conclusion: Dietary manipulation led to significant weight loss and favourable metabolic effects. These beneficial changes did not lead to a reduction in aortic stiffness or pressure wave reflection despite a fall in central aortic blood pressure.

Introduction

Premature large artery stiffening, independent of other classical cardiovascular risk factors, is increasingly considered to be a major contributor to the development of cardiovascular disease in type 2 diabetes.[1] Increased aortic

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1872-9312/$ – see front matter © 2010 Association for Research into Arterial Structure and Physiology. Published by Elsevier B.V. All rights reserved.
doi:10.1016/j.artres.2010.04.001

pulse wave velocity (PWV) is considered to be the gold standard, non-invasive measure of large artery stiffness and is an independent predictor of cardiovascular morbidity and mortality both in healthy, aging adults[2] and in other higher risk populations including hypertension,[3] end-stage renal disease[4] and type 2 diabetes.[5] Recent evidence also supports the concept that central aortic pressure is more closely related to the development of hard cardiovascular outcomes than is brachial artery pressure[6] and furthermore, in diabetes, left ventricular mass is more strongly associated with central pulse pressure than peripheral pulse pressure.[7]

Obesity and hypertension are two key modifiable cardiovascular risk factors that commonly coexist in type 2 diabetes and contribute to increased arterial stiffening and elevated central aortic pressure. Although several studies have established a link between obesity and premature arterial stiffening,[8,9] there has been relatively little study of the specific effects of weight loss on arterial stiffness or central pressure in established type 2 diabetes.

As well as conventional lifestyle intervention, pharmacological therapies are increasingly used to combat obesity. Rimonabant is a cannabinoid-1 receptor blocker that induces weight loss and improves the cardiovascular risk profile, glycaemia and insulin sensitivity in diabetic subjects.[10] Because of concerns relating to depression and suicidal risk, rimonabant's license was withdrawn by the European regulatory authorities in 2008 but there is still interest in this therapeutic class with other agents in development. The endocannabinoid system, consisting of cannabinoid type 1 (CB1) receptors and endogenous ligands is expressed widely, not only in the central nervous system but also in peripheral organs including visceral adipose tissue.[11] In addition, CB1 receptors are also widely expressed in the heart and vasculature and the endocannabinoid system has been implicated as a physiological regulator of arterial tone and blood pressure.[12] To date, there has been little study in humans of the effects of cannabinnoid ligands or cannabinoid receptor blockers on large artery haemodynamics.

The aims of the present study were therefore to examine the effects of weight loss induced by dietary manipulation alone or in combination with rimonabant on central arterial pressure, wave reflection and arterial stiffness in obese subjects with established type 2 diabetes.

Methods

Study design and subjects

Twenty-nine subjects (age range 30–72yrs) (13 male, 16 females) with type 2 diabetes (13 insulin-treated) were recruited from the multidisciplinary diabetes clinic at Torbay Hospital, a UK district general hospital. All subjects were obese with a body mass index of greater than 30 Kg/m^2 and had expressed the desire to lose weight. In an open design, all subjects were studied before, during and after 6 months dietary and lifestyle intervention, either alone (9 subjects) or in combination with rimonabant therapy, 20 mg once daily (20 patients). The decision, whether to intervene with dietary intervention alone or in combination with rimonabant was a clinically-based decision, also taking into account patient preference for pharmacological intervention.

At baseline, all subjects received dietary and lifestyle advice from a specialist diabetes dietician, having completed a 5 day food diary, and were prescribed an individualised 600–800 kcal deficit diet based on healthy eating and portion control. Patients were followed-up during the trial with monthly telephone consultations and with outpatient clinic reviews at 3 and 6 months. Patients with clinical or echocardiographic evidence of left ventricular impairment, peripheral vascular disease or significant renal impairment (estimated GFR$<$30 ml/min) were excluded. All subjects had been receiving a stable regime of blood glucose-lowering treatment for at least 3 months prior to study entry. All subjects were studied at baseline and then at 3 and 6 months following the weight loss intervention. Study measurements and blood samples were undertaken in the morning after a 12 h fast and medications were omitted on the morning of study.

Aortic and brachial pulse wave velocity (PWV) and arterial pulse wave analysis were performed in all subjects. After 10 min supine rest, blood pressure was measured in the dominant arm and radial waveforms were recorded for pulse wave analysis. Following a further 10 min of supine rest, carotid, femoral and radial artery waveforms were recorded for the measurement of carotid to femoral and carotid to brachial PWV. Finally, fasting blood samples (10 ml venous blood for each subject) were drawn on the morning of study. The study had approval from the local research ethics committee, together with clinical trial authorisation. All subjects gave informed consent to participate in the study.

Vascular measurements

Blood pressure measurement

Blood pressure (BP) was recorded in duplicate after 10 min rest at the brachial artery of the dominant arm using a validated semi-automated osscilometric device in the supine position. All hemodynamic measurements were recorded in a quiet, temperature-controlled room. All patients were obese and an appropriate blood pressure cuff size was used.

Pulse wave analysis

Pulse Wave Analysis was performed using the Sphygmocor system (SphygmoCor, Atcor Medical, Sydney, Australia) as previously described.[13] Briefly, this method allows non-invasive generation of a central aortic waveform from that recorded at the radial artery, using a validated generalised transfer function.[14] The augmentation index (defined as the difference between the second and first peaks of the central arterial waveform, expressed as a percentage of the pulse pressure) was determined as a measure of systemic stiffness and taken from the ascending aortic waveform.

Pulse wave velocity (PWV)

Pulse Wave Velocity is the gold standard procedure and validated method for assessing arterial stiffness.[15] In brief, aortic and brachial pulse wave velocity was measured as the time taken for the pulse to travel from a three lead electrocardiogram-gated signal to the first upstroke of the pulse wave at the carotid, radial and femoral site.

Between-observer variation and within-observer variation was consistent with previously published data.[15]

Statistical analysis

All statistical analyses were performed using SPSS (version 14) for Windows. Data are expressed as mean values ± SD. Paired *t*-tests were used to evaluate differences between group means in the same subjects over time for normally distributed data. Correlation between variables was evaluated using Spearman's and Pearson's correlation coefficients and by stepwise multiple regression analysis. A p value of less than 0.05 was considered significant.

Results

Baseline characteristics are summarized in Table 1 with means ± SD. Age of subjects was 57 ± 11 yrs, duration of diabetes was 6 ± 6 years and body mass index (BMI) was 38 ± 5 Kg/m^2. Thirteen of the group were males and 16 were females. Thirteen out of 29 were receiving insulin therapy. There was 1 active smoker in the group. With regards to diabetic complications, 4 had retinopathy, 6 had peripheral neuropathy, 5 had microalbuminuria and 2 had stable ischemic heart disease. Twenty-seven subjects were receiving anti-hypertensive medications for hypertension.

The effects of the dietary intervention for all subjects (rimonabant with diet and diet-alone subjects combined) on physical, biochemical and arterial measurements are also shown in Table 1. All subjects completed the study with the exception of 1 subject in the diet-alone sub-group who failed to attend for the final study visit. One subject discontinued rimonabant treatment at 3 months after developing side-effects of nausea. Over the 6 month period, there were reductions in body weight (104 ± 21 versus 107 ± 21 Kg, $p < 0.001$) and waist circumference (120 ± 12 versus 122 ± 13 cm, $p < 0.001$) and improvements in HbA1c (7.3 ± 1.4 at 3 months, $p < 0.01$ and 7.4 ± 1.5 at 6 months, $p = 0.06$ versus 7.7 ± 1.5% at baseline) and HDL cholesterol (1.3 ± 0.2 versus 1.2 ± 0.3 mmol/L, $p < 0.001$). and HDL cholesterol (1.3 ± 0.2 versus 1.2 ± 0.3 mmol/L, $p < 0.001$). For the 13 subjects receiving insulin therapy, mean insulin dose fell from 116 ± 59 units/day at baseline to 102 ± 71 units/day after 6 months ($p < 0.05$). In addition, aortic diastolic pressure (82 ± 10 versus 85 ± 8 mmHg, $p < 0.05$) and heart rate (70 ± 10 versus 74 ± 12 beats/min, $p < 0.001$) were lower at 6 months in comparison with baseline, despite unchanged peripheral blood pressure or mean arterial pressure. However, there were no statistically significant changes to wave reflection (augmentation index) or arterial stiffness (aortic or brachial artery PWV) during the study.

The whole group was also divided in order to analyse the subjects receiving rimonabant separately from those receiving dietary intervention alone. In the rimonabant-treated patients ($n = 20$), weight was reduced from 112 ± 21 Kg at baseline to 107 ± 21 Kg after 6 months ($p < 0.001$) and this was accompanied by a reduction in waist circumference from 124 ± 13 cm to 121 ± 13 cm ($p < 0.05$). Nine out of 20 patients lost more than 5% of body weight over the 6 month treatment period and 2 out of 20 lost more than 10% of body weight. Weight changes were associated with a reduction in HbA1c from 8.0 ± 1.6% at baseline to 7.4 ± 1.7% at 6 months ($p < 0.05$) and a rise in HDL cholesterol from 1.2 ± 0.2 mmol/L at baseline to 1.3 ± 0.2 mmol/L at 6 months ($p < 0.01$). Aortic systolic pressure was reduced from 147 ± 21 mmHg at baseline to 142 ± 24 mmHg at 6 months ($p < 0.05$) despite no statistically significant changes to brachial systolic pressure. No significant changes to wave reflection (Augmentation index), brachial or aortic pulse wave velocity (10.7 ± 2.3 m/s at baseline versus 10.3 ± 2.5 m/s at 6 months) were observed over the study period in this group of patients.

Table 1 Physical and biochemical characteristics of subjects at baseline and after intervention (Mean ± SD).

Variable ($n = 29$)	Baseline	3 Months	6 Months
Weight (Kg)	107 ± 21	104 ± 20	104 ± 21 **
Waist circumference (cm)	122 ± 13	120 ± 12	120 ± 12 **
Brachial systolic BP (mmHg)	145 ± 21	145 ± 19	144 ± 26
Brachial diastolic BP (mmHg)	83 ± 8	83 ± 11	81 ± 10
Heart rate (beats/min)	74 ± 12	72 ± 12	70 ± 10 **
Total cholesterol (mmol/L)	4.2 ± 1.0	4.1 ± 0.9	4.4 ± 0.9
LDL cholesterol (mmol/L)	2.2 ± 0.9	2.0 ± 0.7	2.4 ± 0.9
HDL cholesterol (mmol/L)	1.2 ± 0.3	1.3 ± 0.3	1.3 ± 0.2 **
Triglyceride (mmol/L)	1.7 ± 1.0	1.7 ± 1.0	1.7 ± 0.8
HbA1c (%)	7.7 ± 1.5	7.3 ± 1.4**	7.4 ± 1.5
Mean arterial pressure (mmHg)	105 ± 13	106 ± 14	105 ± 3
Central pulse pressure (mmHg)	48 ± 17	44 ± 26	47 ± 16
Aortic systolic BP (mmHg)	133 ± 22	129 ± 29	133 ± 24
Aortic diastolic BP (mmHg)	85 ± 8	85 ± 11	82 ± 10 *
Augmentation Index (%)	28 ± 11	27 ± 10	28 ± 10
Aortic PWV (m/s)	10.3 ± 2.2	10.1 ± 2.5	9.9 ± 2.4
Brachial PWV (m/s)	8.3 ± 1.0	8.6 ± 1.3	8.4 ± 1.0
Insulin dose (units/day)	116 ± 59	—	102 ± 71 *

*$p < 0.05$.
**$p < 0.01$ in comparison with baseline.

Multiple regression analysis to determine predictors of aortic PWV

In univariate analyses, for subjects at baseline, BMI correlated with aortic PWV ($r = 0.52$, $p < 0.01$), mean arterial pressure ($r = 0.55$, $p < 0.01$), aortic systolic pressure ($r = 0.54$, $p < 0.01$) and central pulse pressure ($r = 0.43$, $p < 0.01$).

In order to determine independent predictors of aortic PWV in obese diabetic subjects, stepwise multiple regression analysis was performed with aortic PWV as the dependent variable and several potential predicting independent variables (age, mean arterial pressure, HbA1c, BMI and triglyceride) included. This analysis revealed age, BMI and triglyceride concentration to be independent predictors of aortic PWV (Table 2).

Discussion

In this study of obese subjects with type 2 diabetes, we found body mass index to be closely and independently associated with aortic PWV, a finding that supports current evidence suggesting that obesity is an important contributor to premature atherosclerosis and large artery stiffening in diabetes.[8,9] However, we were unable to demonstrate reductions in arterial stiffness or pressure wave reflections in our subjects following a dietary programme leading to significant intentional weight loss over a 6 month period. Significant reductions in aortic diastolic pressure (all subjects) and aortic systolic pressure (rimonabant-treated subjects only) despite no changes in peripheral blood pressure or mean arterial pressure were observed during the study.

To date, there has been relatively little study of the effects of weight loss intervention on arterial stiffness in established diabetes. In obese subjects without diabetes, arterial elasticity as measured by pulse wave contour analysis was improved following 6 months of nutritional and exercise intervention,[16] and in obese subjects with prediabetes, carotid artery distensibility was increased following 6 months of lifestyle intervention.[17] In a study of 38 obese patients with type 2 diabetes of less than 5 years duration, Barinas-Mitchell et al. observed that intentional weight loss through lifestyle intervention led to a reduction in aortic stiffness independent of arterial blood pressure change.[18] In that study, a significant improvement in aortic pulse wave velocity after 1 year of weight loss intervention involving dietary intervention with or without orlistat therapy in type 2 diabetic subjects was reported.[18] These results are in contrast to those from the present study. Possible explanations for this discrepancy include differences in patient characteristics (our subjects had on average a longer duration of diabetes with more microvascular complications, higher systolic blood pressure and approximately 50% were insulin-treated); duration of the study (6 months versus 12 months); proportionately less weight loss in our study subjects; and the use of rimonabant in our study, which may exert pharmacological effects on aortic stiffness through CB1 receptor blockade.

An accumulating body of evidence suggests that both synthetic and endogenous cannabinoids exert meaningful physiological and hemodynamic effects within the cardiovascular system.[11] In particular, endocannabinoids have been shown to exert regulatory effects on blood pressure and peripheral resistance in animal models by acting at CB1 receptors. In hypertensive rats, endogenous cannabinoid ligands lower blood pressure, heart rate and vascular resistance whilst CB1 antagonists increase blood pressure.[19,20] Despite these findings, there has been relatively little study of the cardiovascular effects of cannabinoids or endocannabinoid blockade in humans, although hypotension has been reported with chronic marijuana use.[21] The observations from experimental studies do raise the possibility that CB1 antagonism in humans receiving rimonabant therapy could conceivably increase arterial tone or blood pressure especially in hypertensive individuals. The experience from the RIO-Diabetes trial suggests that brachial artery blood pressure is unchanged following 12 months of rimonabant therapy despite significant weight loss and improved insulin sensitivity.[10] However, in these studies, indices of central arterial pressure, arterial tone or stiffness were not measured. In addition, recent evidence from the STRADIVARIUS trial of patients receiving rimonabant compared with placebo over an 18 month period showed no changes in the primary end-point of atherosclerosis progression as measured by intravascular ultrasound despite improvements in body weight and other metabolic parameters.[22] In the present study, we observed a reduction in aortic systolic pressure after 6 months of rimonabant therapy despite no changes to brachial artery blood pressure. This observed reduction in central pressure might be a consequence of weight loss and beneficial metabolic effects such as improved lipid profile and insulin sensitivity, although no changes to aortic or brachial artery stiffness were observed.

Study limitations

In the present study, the magnitude of weight loss in our subject group overall was relatively small and this may have

Table 2 Stepwise multiple regression analysis with aortic PWV as dependent variable ($R^2 = 0.7$).

Independent variable	Beta	t	*p* value
Age (yrs)	0.65	5.2	<0.001
Body mass index (Kg/m^2)	0.43	3.5	0.002
Triglyceride (mmol/L)	0.27	2.2	0.04
Mean arterial pressure (mmHg)	0.16	0.94	0.36
HbA1c (%)	0.18	1.4	0.17

contributed to our failure to demonstrate any change in pulse wave velocity following the intervention. Our study protocol was not designed to deliver an intensive lifestyle intervention and this probably explains the poorer outcomes in terms of weight loss in the patients not receiving rimonabant. However amongst the rimonabant-treated patients ($n = 20$) there was a much higher degree of weight loss with approximately 50% of patients achieving greater than 5% weight loss. Despite this, we also did not observe a change in pulse wave velocity or obvious trend in this sub-group. Another limitation of the current study relates to the methodology of measurement of carotid-femoral distance in the determination of pulse wave velocity in the more obese subjects. In such subjects, the presence of excessive abdominal adiposity will tend to over-estimate the carotid-femoral distance when determined using a tape measure and thus potentially lead to an over-estimation of velocity. It is possible that this factor may have falsely strengthened the observed relationship between body mass index and pulse wave velocity. Under these circumstances it is possible to employ the use of a calliper to more accurately assess carotid-femoral distance.

In summary, we have demonstrated that in obese subjects with established type 2 diabetes, dietary manipulation, with or without rimonabant, led to significant weight loss, improved glycaemia and favourable changes to the lipid profile. These beneficial effects did not lead to a reduction in large artery stiffness or wave reflection despite a fall in central aortic blood pressure.

Disclosure statement

AC,SB and CH have nothing to disclose. JS has received honoraria for lecturing and an unrestricted educational grant from Sanofi Aventis.

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