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Endothelial dysfunction associated with obesity and the effect of weight loss interventions

S. M. P. Kerr, M. B. E. Livingstone, T. A. McCrorie and J. M. W. Wallace*
Northern Ireland Centre for Food and Health, University of Ulster, Coleraine BT52 1SA, UK

Endothelial damage is central to the initiation and progression of atherosclerosis, while in addition vascular endothelial cells secrete several anti-atherogenic substances including the potent vasodilator nitric oxide. Increased adhesion molecule expression, in response to pathophysiological stimuli is perhaps the earliest indicator of compromised endothelial integrity. Obesity and adiposity are associated with an increased risk of CVD, influencing disease progression via a number of mechanisms, including enhanced endothelial activation. This review discusses possible mechanisms linking adiposity and more specifically regional fat depots with endothelial function and evaluates studies investigating the effect of weight loss on endothelial function, assessed by biochemical and physiological measurements. Overall, the research to date suggests that visceral adiposity is a stronger predictor of endothelial activation than overall adiposity, possibly mediated via the action of NEFA in circulation. While in general there is a suggestion that weight loss is associated with significant improvements in endothelial function, this is not apparent in all interventions and published literature to date provides less than convincing evidence for the effects of weight loss on endothelial activation.

Endothelial function: Endothelial activation: Weight loss: Body composition

CVD account for approximately 4·3 million deaths each year within Europe and are the principal cause of mortality among men and women[1]. CVD presents mainly as CHD and stroke, end products of atherosclerosis, in which the artery wall thickens as a result of a build-up of cells and fatty materials, such as cholesterol. CHD is attributable for about half of all CVD-related deaths in the UK[1]. Numerous non-modifiable risk factors, including age, gender, race and genetic disposition, and modifiable risk factors, including physical inactivity, smoking, diabetes mellitus and obesity, among others, can significantly increase the risk of developing CVD. Management of modifiable risk factors is a primary strategy for stemming the onset of CVD and/or slowing the progression of disease.

Obesity and adiposity, major modifiable CVD risk factors, have become the subject of much research in recent times. This high level of interest may be partly attributed to the fact that the prevalence of obesity has risen within the UK and Ireland, and indeed throughout the world, to epidemic proportions[2]. According to the WHO, obesity is defined as having a BMI greater than 30 kg/m^2. However, BMI cut-offs do not take into consideration that an individual may be small in stature and their total body mass may be made up predominantly by muscle mass. Since BMI is based on one's height and overall weight, this may in turn mistakenly identify an individual as being obese when in fact they may have very low levels of adiposity. The impact of an overweight or obese status on CVD risk is likely to be due to a number of factors. Although not an exhaustive diagram of mechanistic effects of obesity for the development of CVD, Fig. 1 highlights the complexity of interlinking avenues through which obesity can influence the initiation and progression of atherosclerosis.

Obesity is associated with a low-grade inflammatory status which, in turn, can disrupt adipokine production and secretion, leading to deregulation of adipokines. Lowered levels of adiponectin, an adipokine that has protective

***Corresponding author:** Dr Julie M. W. Wallace, fax +44 28 70123023, email j.wallace@ulster.ac.uk

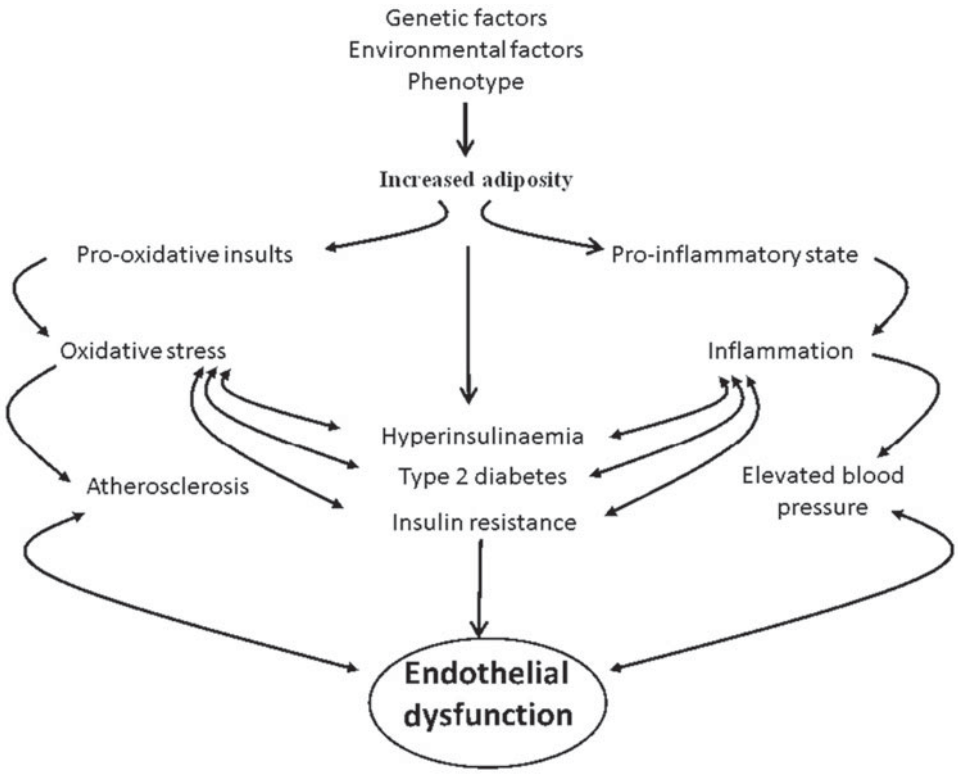

Fig. 1. Relationship between increased adiposity and endothelial dysfunction. Changes in body composition may occur due to a number of interlinking or independent risk factors and the subsequent obese state can have a causal role in a number of factors such as inflammation and oxidative stress, which in turn can cause physiological changes resulting in the end product of CVD. Adapted from Van Gaal *et al.*[3].

effects on the vascular wall by limiting cell adhesion, can result in a reduced cardio-protective effect, thus increasing the chances of complications that are associated with atherosclerosis[4]. Adiposity, and in particular visceral adiposity, may induce insulin resistance[5]. NEFA released from visceral fat to the hepatic portal system can directly affect liver function[6]. In turn, the reduced insulin clearance and increased β-cell secretion alongside reduced insulin action can result in hyperinsulinaemia and thus initiate the early progression of diabetes. Furthermore, oxidative stress, as a result of obesity, can have a role in atherosclerosis[7], leading to oxidation of LDL which allows for rapid uptake by macrophages, thus aiding the progress of atherosclerosis plaque development[8].

In addition, adipose tissue is known to be a multifunctional organ producing and secreting a number of proteins that act directly, either in an auto/paracrine or an endocrine manner[9–12] upon the vasculature and subsequently lay the foundation for adverse cardiovascular events. Differing body composition and in particular different fat depots, i.e. subcutaneous and visceral fat, as opposed to overall obesity, may pose differing risk of adverse cardiovascular events[13–15]. Visceral adiposity has been associated with a clustering of adverse metabolic abnormalities that increase the risk and incidence of CVD[16–18], which may in part be due to the possible regional variations in secretions of proteins[19]. For instance, it has been reported that visceral fat induces increased production of the pro-inflammatory cytokine IL-6 in plasma[15,20], which could increase portal vein concentrations of IL-6[21]. Increases in IL-6 concentrations may subsequently decrease LPL activity and monomeric LPL levels in plasma, which in turn increase uptake of lipids by macrophages[22]. Lipid-laden macrophages play a central role in developing atherosclerotic plaques. In addition, increased production of IL-6, as a direct result of visceral fat drainage to the portal vein, may affect hepatic metabolism and impair insulin signalling (referred to as hepatic insulin resistance)[21]. This hepatic insulin resistance could lead to complications such as hyperglycaemia due to impaired glucose homoeostasis, which may directly induce endothelial dysfunction[23]. Mechanistically, the specific role that hyperglycaemia plays in CVD development remains unclear. A recent study, however, suggests that hyperglycaemia activates the Ca/calcineurin-dependent transcription factor of activated T-cells in arteries sequentially leading to enhanced expression of osteopontin[24], a matrix cytokine that enhances recruitment and retention of macrophages at the site of inflammation[24].

Visceral fat is also purported to be an ectopic fat depot, indicating that there is a reduced ability of subcutaneous fat depots to take up and store circulating TAG fatty acids. This is coupled with excessive release of NEFA[21,25]. Increased levels of NEFA in the circulation can directly affect endothelial function, impairing endothelial-dependent vasodilatation[26], potentially by altering

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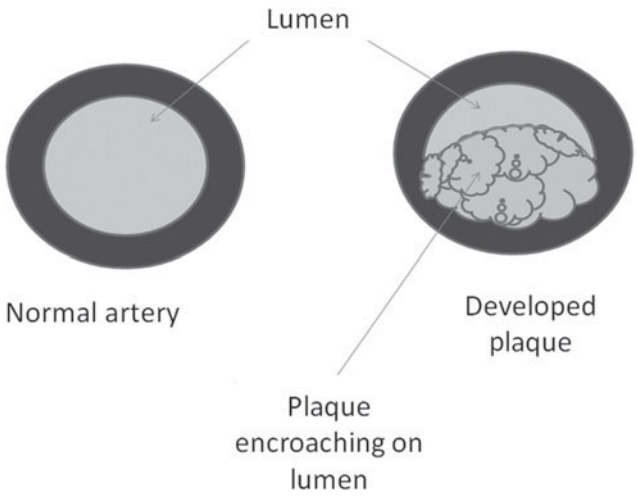

Fig. 2. Cross-section of normal (left) and blocked artery (right). Plaque, made up of fat, cholesterol, Ca and other substances found in the blood, hardens and narrows the arteries, limiting the flow of oxygen-rich blood to organs and other parts of the body. This leads to serious problems, including heart attack and stroke.

vascular reactivity, or through hepatic insulin resistance[27]. A recent review suggests that obesity-associated microvascular dysfunction, associated with cellular defects that influence the balance between endothelial-derived vasodilating and vasoconstrictor effects may be the underlying cause of obesity-associated high blood pressure[28]. The authors propose that a number of factors including NEFA elevation and impaired intracellular insulin signalling may increase production of reactive oxygen species and diminish nitric oxide expression and activity, which may suppress endothelium-derived vasodilation in obese individuals.

Pathogenesis of atherosclerosis

Atherosclerosis is the underlying pathological process in CVD development in which there is increased build-up of fat and cholesterol, among other cellular deposits, in the arterial wall. Subsequently, over time there is a narrowing of the lumen thus reducing the flow of oxygen-rich blood to vital organs throughout the body including the heart and brain (Fig. 2). Central to the integrity of the vasculature is the endothelium. Once considered to be an inert layer of cells acting only as a barrier between circulating blood in the lumen and the vascular wall, the endothelium has recently been the subject of much research with a plethora of functions now attributed to this thin monolayer of cells.

Lining the entire circulatory system, from the heart to the smallest capillary, the endothelium forms the innermost layer of arteries and capillaries, and is therefore situated in the ideal location to sense changes in haemodynamic forces and blood-borne signals, and subsequently respond by releasing vasoactive substances[29]. Adjusting conditions in favour of vascular homoeostasis, the endothelium functions by releasing a variety of paracrine factors that act within the blood vessel wall and lumen[30]. Under normal conditions, these endothelial cell-derived factors maintain vascular tone, blood fluidity and limit vascular inflammation and smooth muscle cell proliferation[30]. When the integrity of the endothelium is compromised, it results in endothelial dysfunction, a state in which the endothelial cells secrete substances that promote atherosclerotic plaque build-up.

Endothelial dysfunction is associated with an imbalance between vasoconstriction and vasodilation, increased endothelial permeability, platelet aggregation, leucocyte adhesion and cytokine expression, which may promote atherosclerosis[31] (Fig. 3). Adhesion of circulating leucocytes to the endothelial cells, prior to sub-endothelial migration, is suggested to be an important early stage in the initiation of atherosclerotic lesions[32] and subsequent cardiovascular events.

Obesity in endothelial activation

Prior to adhesion and migration of leucocytes, the cell-surface expression of adhesion molecules, namely intercellular adhesion molecule 1, vascular cellular adhesion molecule 1 and E-selectin among others, on endothelial cells, are up-regulated[33]. This is referred to as endothelial activation. Activation of endothelial cells is considered a crucial early step in an inflammatory response[34], and indeed may be the earliest detectable indication of endothelial damage, comprising adhesion and transmigration of leucocytes to and across the endothelium. Research has shown that a number of risk factors for CVD, including smoking[35], smoking coupled with hypercholesterolemia[36] and insulin resistance[37], induce endothelial activation. However, currently the role of overweight and obesity, and, in particular, association between specific fat depots in relation to endothelial activation, is not fully established. A number of potential mechanisms through which adipose tissue may initiate endothelial activation have been proposed.

The release of NEFA by adipose tissue can directly result in endothelial dysfunction[25]. An upper-body obese phenotype is associated with greater concentrations of NEFA than obesity of lower extremities[38,39], thus suggesting that visceral and/or trunk fat may have a more marked effect with regard to endothelial dysfunction than fat stored at other sites throughout the body. Furthermore, visceral fat, due to its location and close association with portal circulation, as previously discussed, may have a greater role in endothelial dysfunction, i.e. through hepatic insulin resistance[5,6].

Mathew *et al.*[40] assessing the effects of NEFA at concentrations similar to those observed in obese subjects reported that lipid infusion increased plasma intercellular adhesion molecule 1 and vascular cellular adhesion molecule 1 levels, thus indicating a direct effect on endothelial cell activation. However, in the study by Mathew *et al.*[40] there were no associations between levels of intercellular adhesion molecule 1 or vascular cellular adhesion molecule 1 and BMI, possibly because BMI is a measure of body weight and not adiposity *per se*. Using BMI as a surrogate measure of body fatness would not allow for identification of specific fat depots and therefore associations between

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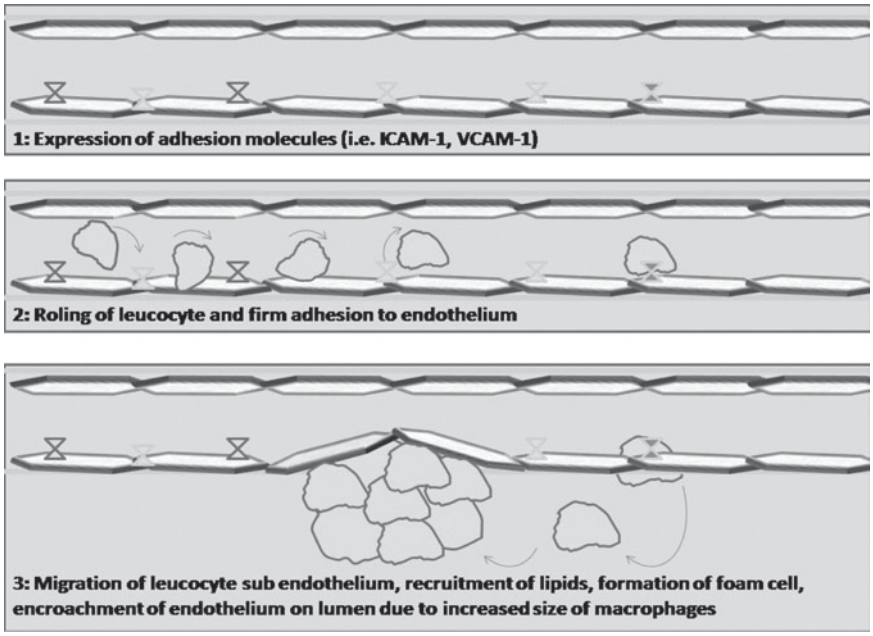

Fig. 3. Initial phases of endothelial dysfunction and subsequent plaque formation leading to atherosclerosis. Damaged endothelial cells express adhesion molecules (intercellular adhesion molecule 1 (ICAM-1) and vascular cellular adhesion molecule 1 (VCAM-1)) (part 1) which recruit leucocytes to the site of injury (this is known as the inflammatory response). Adhesion molecules initiate firm adhesion of the leucocytes to the endothelium (part 2). Once firmly adhering to the endothelial layer, the leucocytes migrate sub-endothelium. When resident in the intima, the leucocytes acquire characteristics of the tissue macrophages, i.e. expressing scavenger receptors that bind lipoprotein particles. This, in turn, gives rise to the formation of an arterial foam cell. The foam cell secretes pro-inflammatory cytokines thus leading to a heightened inflammatory response. As the foam cell increases in size, it encroaches on the lumen and narrows the artery, thus decreasing the amount of blood flow through the artery (part 3).

the specific fat regions and NEFA expression could not be investigated. Clearly, identification of regional fat depots which may contribute to increased levels of NEFA may allow for associations to be drawn between these fat depots, NEFA and endothelial activation and merits further investigation.

Findings have already been reported in animal models of obesity where surgical removal of visceral fat normalised NEFA concentrations in rats[41,42], suggesting that visceral adiposity is important for determining levels of NEFA. If such relationships are confirmed in human subjects then it may be hypothesised that visceral adiposity is a major contributor to endothelial activation via its effect on NEFA concentrations. There are, however, few studies to date in this area. Ybarra *et al.*[43] using liposuction for the removal of abdominal fat reported significant decreases in NEFA concentrations. However, changes in BMI, waist circumference and weight were not associated with decreased levels of NEFA. Furthermore, visceral and subcutaneous fat were removed together making it impossible to establish if the decrease in NEFA concentrations was related to changes in visceral, subcutaneous or total fat removal. That said, however, a study that assessed only the removal of subcutaneous fat via liposuction found that there was no improvement in inflammation and NEFA concentrations[44]. This suggests that the effects seen in the study by Ybarra *et al.*[43], of liposuction on NEFA may be attributed to the removal of visceral as opposed to subcutaneous fat.

Further studies aimed at identifying mechanisms through which obesity induces endothelial activation have reported in obese children that hypertension was the main driver of endothelial dysfunction[45]. Children and adolescents with obesity-related hypertension had higher serum inflammation and endothelial activation markers than normotensive obese subjects despite similar BMI, waist:hip ratio and fat mass. It has been suggested[46] that hypertension is associated with the impairment of endothelium-dependent vasodilation and this appears to represent an accelerated form of dysfunction normally observed with ageing. However, the mechanism through which hypertension may induce such effects in some individuals, but not others, remains to be established. Additionally it is still unclear as to whether in fact hypertension is the cause or effect of endothelial dysfunction. What is evident, however, is that endothelial activation can be present at a very early stage in life. In a more recent study[47] adiposity was associated with higher levels of insulin resistance, E-selectin and soluble vascular cellular adhesion molecule in apparently healthy normal weight children as early as 2–3 years of age and such associations were evident even in children with relatively low levels of adiposity. These studies therefore clearly

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Table 1. Endothelial dysfunction associated with obesity and the effect of weight loss interventions

Method of weight loss (reference)	Total number of subjects (no. of treatment) (*n*)	Duration	Sex	Baseline												Effect of weight loss – % decrease for treatment group									
				Age (years)	SD	BMI (kg/m^2)	SD	WC (m)	SD	WHR	SD	Fat mass (%)	SD	Body fat (%)	SD	ICAM-1	VCAM-1	TNF	IL-6	FMD	PWV	SBP	DBP	Weight	Body fat
Diet only																									
Bergholm *et al.*[48]	47 (23)	6 months	F	(39)	1	(32·3)	0·4	–	–	(0·94)	0·02	–	–	(35·6)	0·4	–	–	–	–	41·0	–	NS	NS	8·3	8·3
				39	1	32·3	0·4			0·95	0·01			36·8	0·5										
Sciacqua *et al.*[49]	28 (28)	4 months	M + F	(42·6)	7·5	(33·1)	4·2	(108·2)	12·1	–	–	–	–	–	–	–	–	–	–	74·3	–	3·7	3·5	16·9	–
Clifton *et al.*[54]	55 (26)	3 months	M + F	(49·3)	8·8	(31·8)	2·8	–	–	–	–	–	–	–	–	10·4	9·3	–	4·9	NS	17·4	5·9	6·3	19·0	–
				47·1	10·3	33·2	3·1																		
Bougoulia *et al.*[50]	71 (35)	6 months	F	(38)	7·1	(37·2)	5·3	(109·3)	12·7	(0·9)	0·05	(56·7)	5·8	(43·3)	5·4	–	–	48·1	87·4	–	–	–	–	23·7	27·5
				35·4	9·2	38·5	7	108·5	10·6	0·9	0·05	57·9	8·2	42·5	8·1										
Esposito[55]	180 (90)	2 years	M + F	(44·3)	–	(29·7)		(92)	–	–	–	–	–	–	–	–	–	–	33·3	–	–	3	3·5	4·3	–
				43·5		28·1		93																	
Raitakari[53]	67 (67)	6 weeks	M + F	(46)	7	(35·2)	5·4	(110)	14	(0·93)	0·08	–	–	–	–	–	–	–	–	60·0	–	8·5	10·0	10·8	–
Diet and exercise combined																									
Hamdy *et al.*[56]	24 (24)	6 months	M + F	(49·3)	1·9	(36·7)	0·9	–	–	(0·92)	0·02	–	–	–	–	5·4	NS	–	–	63·3	–	NS	NS	7·3	–
Pontiroli *et al.*[57]	126 (126)	1 year	M + F	(18–66)	–	(44·3)	0·4	(121·6)	0·9	–	–	–	–	–	–	12·1	–	–	–	–	–	3·5	3·2	17·8	–
Williams *et al.*[51]	73 (73)	6 months	M + F	(35·4)	–	(52·2)		(138)	–	–	–	–	–	–	–	–	–	NS	NS	92·0	–	7·5	5·8	13·6	–
Surgery and diet combined																									
Ziccardi[58]	96 (56)	1 year	F	(35·3)	4·8	(37·2)	2·2	–	–	(0·84)	0·06	–	–	–	–	25·7	28·1	31·0	46·5	–	–	–	–	12·6	–
				34·1	5·2	23·5	1·7			0·72	0·05														
Gokce *et al.*[52]	41 (24)	3 months	M + F	(44)	9	(42)	10	–	–	–	–	–	–	–	–	–	–	–	–	49·9	–	NS	NS	25·0	–

F, female; M, male; WC, waist circumference; WHR, waist hip ratio; ICAM-1, intercellular adhesion molecule 1; VCAM-1, vascular cellular adhesion molecule 1; NS, non-significant; FMD, flow mediated dilation; PWV, pulse wave velocity; SBP, systolic blood pressure; DBP, diastolic blood pressure.

indicate that overweight and obesity are associated with endothelial activation and it is possible that adiposity in the visceral region may be a stronger predictor than overall adiposity of endothelial activation.

Other studies[48–53] have investigated the effects of obesity on endothelial function using physiological measures of the response of the vasculature to the development of cardiovascular problems and symptoms, e.g. the measurement of brachial artery blood flow via flow-mediated dilation to assess endothelial damage, as opposed to measuring markers of endothelial activation. However, such methods measure endothelial dysfunction at a later stage in the atherosclerotic disease process. Since endothelial activation preludes endothelial dysfunction, studies measuring soluble markers of activation may be more useful to identify those at risk of future cardiovascular events early in the disease process.

Weight loss and endothelial function

To our knowledge only eleven intervention studies have investigated the effect of weight loss on endothelial function. The majority recruited subjects aged between 40 and 50 years, mostly female, with only half of the studies including a control group. All studies used BMI as a proxy measure of total body fat, while half of the studies also included waist circumference as an estimate of visceral fat. Only one study measured body fat via direct measures in the form of MRI. Of the studies included, weight loss was achieved by diet only (*n* 6), diet and exercise (*n* 1), surgery only (*n* 2) and surgery followed by diet (*n* 2). Percentage weight loss ranged from 4·3 to 25%, with the duration of intervention ranging from 6 weeks to 2 years.

Overall, the studies in Table 1 suggest improvement in endothelial function following weight loss irrespective of the method of weight loss employed. Few studies to date have used biochemical assessment of endothelial activation[54,56–58], and although the limited available data suggest that even modest weight loss (7·3%) is accompanied by significant decreases in intercellular adhesion molecule, this clearly requires further confirmation. A larger number of studies have used physiological measures of endothelial function[48,49,51–57], (flow-mediated dilation *n* 7; pulse wave velocity *n* 1; blood pressure *n* 9), but the findings are inconsistent and contradictory. For example, in one study by Gocke *et al.*[52] a 25% weight loss was associated with a non-significant change in systolic blood pressure or diastolic blood pressure, whereas Raitakari[53] showed that a 10% weight loss was accompanied by a 60% decrease in flow-mediated dilation and significant improvements in systolic and diastolic blood pressure. The lack of significant effects of weight loss on blood pressure in three of these studies[48,52,56] is possibly due to the inclusion of normotensive subjects.

Decreases in systolic blood pressure of 4–12 mmHg and in diastolic blood pressure of 3–9 mmHg were observed in six of the eleven weight loss intervention studies even when only modest weight loss was achieved[49,51,53–55,57]. Small changes in blood pressure are reported to have clinical benefits. For example, a long-term difference of 5–6 mmHg in usual diastolic blood pressure is associated with 35–40% lower incidence of stroke and 20–25% decrease in CHD[59].

Overall, the paucity of data precludes definitive conclusions about the relationship between weight loss and improvements in endothelial function. This can only be addressed by well-designed intervention studies that include robust measures of body composition and both physiological and biochemical markers of endothelial function.

Discussion

As previously discussed, endothelial dysfunction is a precursor of the initiation and progression of atherosclerosis. Identification of endothelial dysfunction at an early stage may allow the development of strategies to arrest disease progression.

Despite consistent evidence from observational studies linking obesity and adiposity with altered arterial homoeostasis and endothelial dysfunction[60], overall the published literature to date provides less-than-convincing evidence for the effects of weight loss on endothelial activation. Any improvements observed are not consistent across all interventions. These inconsistencies may be at least partially attributed to differing study protocol and study populations. For example, some studies are of short duration (6 weeks) and studies utilise only physiological or biochemical measures of endothelial function rather than employing a combination of both physiological and biochemical measures. As previously discussed, visceral fat is a key determinant of cardiovascular risk[16–18]. Therefore, it is imperative that future intervention studies in this area include robust measures of total and regional body composition (i.e. fat and fat-free mass) rather than relying on proxy measures such as BMI and waist circumference.

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