REVIEW

Obesity and Thrombosis

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Objectives. To describe the pathophysiological mechanisms by which obesity increases the propensity to thrombosis, the leading cause of death in the Western World, with particular emphasis on the role of inflammation, oxidative stress, dyslipidaemia, insulin resistance and the coagulation cascade.

Design. Review article.

Materials and methods. Medline (1966–2005) and Cochrane library review of literature examining the relationship between obesity and thrombosis. Search terms included obesity, overweight, body mass index, thrombosis, cardiovascular disease, venous thromboembolism, peripheral arterial disease, and coronary heart disease.

Results. Obesity is an important and growing public health issue that is estimated to affect more than half of the UK adult population. Obesity, in particular central (visceral) obesity, is associated with significant, and largely preventable, morbidity and mortality including an increased incidence and prevalence of arterial and venous thrombotic events. The various mechanisms by which obesity may cause thrombosis include: the actions of so-called adipocytokines from adipose tissue, e.g. leptin and adiponectin; increased activity of the coagulation cascade and decreased activity of the fibrinolytic cascade; increased inflammation; increased oxidative stress and endothelial dysfunction; and disturbances of lipids and glucose tolerance in association with the metabolic syndrome.

Conclusions. Obesity appears to be associated with thrombosis via several mechanisms. These pro-thrombotic factors are all improved by weight loss.

Keywords: Obesity; Thrombosis; Leptin; Adiponectin; Venous thromboembolism; Metabolic syndrome.

Introduction

Two-thirds of all men and half of all women in England (equivalent to approximately 24 million people) are either overweight or obese.¹ In England, obesity accounts for approximately 18 million days of sickness absence and 30,000 premature deaths each year.² It is estimated that the annual cost of treating obesity in the UK is £500 million and the wider costs to the economy in terms of lower productivity and lost output are £2 billion each year.²

Obesity and overweight are associated with increased risk of coronary heart disease (CHD), peripheral arterial disease (PAD), stroke (CVA), and venous thromboembolism (VTE).³–⁶ However, it remains to be determined whether obesity is a truly independent risk factor or acts through its association with several other well-known cardiovascular risk factors (such as insulin resistance/diabetes and dyslipidaemia). Obesity also plays a central role in the development of the metabolic syndrome, a cluster of cardiovascular risk factors, which leads to an approximately 3-fold risk of CHD and CVA.⁷

This article reviews what is currently known about the pathophysiological mechanisms by which obesity increases this propensity to thrombosis. In particular, we discuss the role of inflammation, oxidative stress, dyslipidaemia, insulin resistance, as well as direct effects on the coagulation cascade.
Methods

We performed a MEDLINE (1966–2005) and Cochrane library search looking for articles relating to the relationship between obesity, overweight and thrombosis. These terms were linked with the following: coagulation, thrombosis, fibrinolysis, cardiovascular disease, coronary heart disease, stroke, peripheral vascular disease and peripheral arterial disease, deep venous thrombosis and venous thromboembolism. Further articles were identified by following MEDLINE links, by cross-referencing from the reference lists of major articles and by following citations for these studies.

Results

The anatomy of obesity and cardiovascular risk

Obesity is defined as an excess of body fat and usually described by the body mass index (BMI) which is calculated as the square of weight/height. The World Health Organization (WHO) definition of overweight is BMI > 25 kg/m² and of obesity BMI > 30 kg/m². Two patterns of obesity have been distinguished for the purposes of risk factor assessment; namely, central (visceral) obesity and peripheral obesity. Central obesity is defined as deposition of fat around the trunk and in the visceral adipose tissue. It is more common in men and carries a higher risk of CHD, as well as various metabolic derangements including dyslipidaemia and glucose intolerance. Peripheral obesity is accumulation of fat predominantly in the gluteo-femoral area. It is more common in women and is less strongly associated with cardiovascular risk.

The use of BMI alone as a marker of overweight and obesity is limited for, although it correlates well with total body fat content in adults, it fails to consider the distribution of that fat. In view of the relationship between central obesity and CHD, other methods of defining obesity have been used; for example, the waist circumference (WC) and waist-to-hip ratio (WHR). Men with a WC of >102 cm (>40 inches) and women with a WC > 88 cm (>35 inches) have a higher risk of CHD, and a WHR of >0.92 carries a nearly 3-fold increased risk.

The adipocyte and thrombosis

Adipose tissue is not only an energy storage tissue, but also a metabolically active organ secreting hormones, cytokines and growth factors that act in an autocrine, paracrine or endocrine manner (Table 1).

Table 1. Substances potentially involved in thrombosis, secreted by adipose tissue

<table>
<thead>
<tr>
<th>Substance</th>
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<tr>
<td>Leptin</td>
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<tr>
<td>Adiponectin</td>
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<tr>
<td>Resistin</td>
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<tr>
<td>Plasminogen Activator Inhibitor-I (PAI-1)</td>
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<tr>
<td>Tissue factor</td>
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<td>Angiotensin II and other substances of the RAS</td>
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<tr>
<td>Non-Esterified Free Fatty Acids (NEFAs)</td>
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<tr>
<td>Tumour Necrosis Factor-α (TNFα)</td>
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<tr>
<td>Transforming Growth Factor-β (TGFβ)</td>
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<tr>
<td>Interleukin-6 (IL-6)</td>
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RAS = Renin Angiotensin System.

These moieties influence and help control energy homeostasis, glucose and lipid metabolism, and vascular homeostasis.

Leptin

Although expressed in many tissues including muscle, placenta and gastric epithelium, leptin is predominantly produced and secreted from adipose tissue. The majority of leptin studies have been performed on animals. There is much evidence supporting the theory that leptin acts via the hypothalamus to suppress food intake and to increase energy expenditure by modulating glucose and fat metabolism, and enhancing thermogenesis. Leptin also has direct effects on many peripheral tissues, including muscle and pancreatic beta cells.

Hyperleptinaemia has been implicated in the development of insulin resistance, and carries an increased incidence of ischaemic stroke and acute myocardial infarction (MI), independent of other risk factors. To our knowledge, there are no published studies examining the relationship between leptin and VTE or PAD.

Most obese people have high circulating leptin concentrations that should decrease caloric intake, through a reduction in appetite and also increased energy expenditure. It is, therefore, generally accepted that the overweight and obese are insensitive to these effects of blood-borne leptin. Serum leptin concentrations decrease following weight loss due to dieting. Leptin levels in the cerebrospinal fluid of obese patients are generally much lower than serum levels suggesting that leptin is transported through the blood-brain barrier via a saturable transport system. Leptin resistance could, therefore, be caused by abnormalities in that system, in the leptin receptor, or in post-receptor signalling mechanisms.

The leptin receptor is present in many tissues, including platelets. Leptin promotes human platelet aggregation by potentiating the normal platelet response to its agonists adenosine diphosphate and thrombin. This has recently been suggested as a mechanism for acute
Obesity can be considered a chronic, low-grade inflammatory state, as demonstrated by increased levels of the pro-inflammatory cytokines IL-6 and TNF-α, and therefore, the primary physiological inhibitor of fibrinolysis in vivo. PAI-1 is produced in several tissues including liver, spleen and adipocytes. Elevated PAI-1 levels compromise the normal clearance of fibrin and consequently promote thrombosis. PAI-1 levels are positively correlated with obesity (measured by BMI, WC and WHR), insulin resistance, and triglyceride levels and PAI-1 levels are significantly reduced by weight loss in obese individuals. High PAI-1 concentrations have been found in patients with recent MI, chronic CHD, PAD, DVT, and CVA. Several factors increase PAI-1 expression and synthesis in adipose tissue, including free fatty acids, triglycerides, insulin, TGFβ, angiotensin II, CRP and TNFα. Thus, the increased levels of PAI-1 found in obesity may predispose to micro- and macro-vascular, arterial and venous, thrombosis.

**Fibrinogen**

Hyperfibrinogenaemia is associated with an increased prevalence and incidence of primary and recurrent CHD, CVA, PAD and VTE and correlates with measures of obesity in several studies, especially in women. Fibrinogen promotes arterial and venous thrombosis through increased fibrin formation, platelet aggregation and plasma viscosity; and promotes atherosclerosis through vascular smooth muscle and endothelial cell proliferation.

**Tissue factor (TF)**

The coagulation cascade is initiated when TF is exposed to blood and binds with factor VIIa. Obese patients exhibit increased TF-mediated coagulation, with raised adipocyte and monocyte TF expression secondary to elevated levels of CRP, TGFβ, TNFα, angiotensin II and insulin.

**Factor VII and VIII**

High factor VII and factor VIII levels correlate with measures of obesity, and an increased risk of CHD and stroke in some, but not all, studies. Factor VIII, but apparently not VII, is strongly associated with raised adipocyte and monocyte TF expression secondary to elevated levels of CRP, TGFβ, TNFα, angiotensin II and insulin. High triglycerides and low high density lipoprotein (HDL) cholesterol, the most common lipid disturbances found in obesity, are also found with high factor VII and VIII levels.

### The relationship between obesity and coagulation and fibrinolysis (Fig. 1)

**Plasminogen activator inhibitor-1**

PAI-1 inhibits tissue plasminogen activator (tPA), which cleaves plasmin from plasminogen and is, therefore, the primary physiological inhibitor of fibrinolysis in vivo. PAI-1 is produced in several tissues including liver, spleen and adipocytes. Elevated PAI-1 levels compromise the normal clearance of fibrin and consequently promote thrombosis. PAI-1 levels are positively correlated with obesity (measured by BMI, WC and WHR), insulin resistance, and triglyceride levels and PAI-1 levels are significantly reduced by weight loss in obese individuals. High PAI-1 concentrations have been found in patients with recent MI, chronic CHD, PAD, DVT, and CVA. Several factors increase PAI-1 expression and synthesis in adipose tissue, including free fatty acids, triglycerides, insulin, TGFβ, angiotensin II, CRP and TNFα. Thus, the increased levels of PAI-1 found in obesity may predispose to micro- and macro-vascular, arterial and venous, thrombosis.

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acute phase proteins such as CRP. This pro-inflammatory state is attenuated by weight loss.\textsuperscript{44,45} As well as its direct effects, inflammation may cause thrombosis indirectly by inducing oxidative stress and endothelial dysfunction.\textsuperscript{46}

C-reactive protein (CRP)
Elevated CRP is a powerful marker of increased atherothrombotic events,\textsuperscript{40,47} correlates positively with BMI, and visceral fat accumulation,\textsuperscript{40,48} and may contribute to thrombosis via several mechanisms. Specifically, it may (a) increase endothelial adhesion molecule expression, (b) stimulate macrophages to produce cytokines, such as IL-6 and TNF\textsubscript{a}, which may render an otherwise stable atherosclerotic plaque vulnerable to rupture and (c) induce TF production by monocytes.\textsuperscript{25,46,49–51}

Interleukin-6 (IL-6)
IL-6 is produced by adipose tissue, monocytes and macrophages, endothelial cells, and skeletal and smooth muscle cells. Up to one-third of circulating IL-6 comes from adipose tissue.\textsuperscript{10,40} IL-6 production is increased by IL-1 and TNF\textsubscript{a}, and is associated with thrombotic cardiovascular events.\textsuperscript{52} IL-6 levels are positively associated with BMI, WC and WHR, and also with measures of insulin resistance.\textsuperscript{4,48} IL-6 levels decrease with weight loss.\textsuperscript{52} IL-6 increases plasma lipids and glucose by inducing insulin resistance through decreasing insulin signalling in peripheral tissues.\textsuperscript{10,12} IL-6 may also promote thrombosis indirectly through increasing platelet count and aggregation, hepatic synthesis of fibrinogen and CRP, endothelial adhesion molecule expression, and decreasing adiponectin secretion.\textsuperscript{16,52}

Tumour necrosis factor-\alpha (TNF\textsubscript{a})
Adipocyte TNF\textsubscript{a} secretion is positively correlated with obesity and reduces with weight loss.\textsuperscript{46,52} Adipocyte TNF\textsubscript{a} receptor expression also correlates with obesity,\textsuperscript{10,46} and may contribute to insulin resistance directly by inhibiting insulin receptor activity and signalling, and indirectly by increasing serum non-esterified fatty acids (NEFAs).\textsuperscript{10,21,22,29} NEFAs induce

Fig. 1. Obesity and the coagulation cascade: the different pathways in the coagulation and fibrinolytic cascades that may be affected by obesity.
insulin resistance in a variety of tissues. TNFα increases the hepatic synthesis of NEFAs and also reduces the uptake and storage of NEFAs in adipose tissue.¹⁰,⁵⁰ TNFα stimulates leptin production and reduces adiponectin secretion from adipose tissue, induces PAI-1 expression in adipose tissue, and promotes endothelial adhesion molecule expression.¹⁰,¹⁶

The relationship between obesity, oxidative stress, endothelial dysfunction and thrombosis (Fig. 2)

Oxidative stress
Oxidative stress is defined as a state where the normal balance between the body’s pro-oxidant and antioxidant systems is disturbed in favour of oxidation.⁵³,⁵⁴ Oxidative stress from reactive oxygen species production promotes endothelial dysfunction, platelet aggregation, and thrombus formation.⁵⁵ It also impairs both pancreatic insulin secretion and, in rodent studies, it reduces glucose transport in muscle and adipose tissue.⁵⁶ F2-isoprostanes are products of the peroxidation of arachidonic acid, catalysed by free radicals.⁵³,⁵⁷ Measurement of F2-isoprostanes is currently the most accurate method available to quantify oxidative stress in humans.⁵⁸ Increased CRP is also found with significant elevations in isoprostanes.⁵³,⁵⁷ F2-isoprostanes themselves induce vasoconstriction and can amplify the response of human platelets to other agonists.⁵⁹,⁶⁰ Enhanced isoprostane formation is strongly correlated with increasing BMI and WHR.⁵⁹,⁶⁰ Many of the metabolic abnormalities found with obesity are also associated with increased oxidative stress.⁶⁰ NEFAs, TNFα, and oxidised LDL (low density lipoprotein) cholesterol may all increase the production of reactive oxygen species, superoxide and H₂O₂ in the endothelium.⁴⁶,⁶¹ Reactive oxygen species themselves serve as a precursor to oxidised LDL formation, essential to the development of atherosclerotic lesions.⁴⁶ Protein glycation and glucose autoxidation in hyperglycaemia also cause oxygen free radical formation.⁵⁴ HDL particles, which are commonly reduced in obesity-associated dyslipidaemia, have anti-inflammatory and potent anti-oxidative activity, and indeed dyslipidaemia has been found to increase isoprostanes.⁵⁴,⁶⁰ As mentioned previously, inflammation and raised levels of CRP, IL-6 and TNFα also contribute to oxidative stress in obesity. This is consistent with studies that have found elevated levels of F2-isoprostanes in several

Fig. 2. Oxidative stress and obesity: how obesity may lead to oxidative stress.
inflammatory diseases.\textsuperscript{57} Furthermore, antioxidant defence mechanisms are reduced in obesity, including decreased erythrocyte glutathione and glutathione peroxidase.\textsuperscript{62}

**Endothelial dysfunction**

Endothelial dysfunction is characterised by a disturbance in the normal balances between vasoconstrictors and vasodilators, growth promoters and inhibitors, pro- and anti-atherogenic processes, and pro- and anti-coagulant factors.\textsuperscript{61} Endothelial dysfunction is central to the development and progression of atherosclerosis, and enhances the risk of future cardiovascular events.\textsuperscript{61} Endothelial dysfunction is present in overweight patients, especially those with visceral obesity and insulin resistance, and weight loss leads to an improvement in endothelial function.\textsuperscript{52,61,63} As described above, low levels of adipocyte-derived circulating and intra-mural adiponectin may favour endothelial damage; possibly through a decrease in nitric oxide (NO) production in association with an increase in reactive oxygen species.\textsuperscript{55} NO not only reduces vascular smooth muscle cell migration and growth, platelet aggregation, monocyte and macrophage adhesion, and inflammation, but also causes vasodilatation.\textsuperscript{61} Decreased NO production may therefore contribute to increased platelet activation and arterial thrombosis, as well as increased atherogenesis.

**Renin-angiotensin system**

In obese rodents, the renin-angiotensin system (RAS) is up-regulated in adipose and non-adipose tissue.\textsuperscript{64} Renin, angiotensinogen, angiotensin (AT) I and II, and angiotensin converting enzyme (ACE) are all produced by adipocytes.\textsuperscript{60} AT II promotes tissue superoxide production, increases LDL uptake by macrophages and, in vessel walls, has significant pro-inflammatory actions.\textsuperscript{65} Specifically, AT II increases the production of reactive oxygen species, inflammatory cytokines and adhesion molecules leading to atherosclerotic plaque destabilization.\textsuperscript{64,65}

The metabolic syndrome is defined as the presence of three or more of:\textsuperscript{66}

1. Fasting glucose $> 6.1$ mmol/L ($> 110$ mg/dL)
2. Triglycerides $> 1.69$ mmol/L ($> 150$ mg/dL)
3. HDL cholesterol $< 1.04$ mmol/L ($< 40$ mg/dL) in men; and $< 1.29$ mmol/L ($< 50$ mg/dL) in women
4. Blood pressure $> 130/85$ mmHg
5. Abdominal obesity: WC $> 102$ cm (40 inches) in men; and $> 88$ cm (35 inches) in women

Patients with the metabolic syndrome have a 3-fold increased risk of CHD and stroke.\textsuperscript{7,67} Overall, around a quarter of adults in Europe and North America have the metabolic syndrome, rising to around 40% of those aged over 40 years in one study.\textsuperscript{68–71} The Women’s Ischemia Syndrome Evaluation (WISE) study of 780 women referred for coronary angiography found that 76% of obese, compared with 28% of normal BMI, subjects had the metabolic syndrome or diabetes.\textsuperscript{67} Significantly, weight loss usually improves all aspects of the metabolic syndrome.\textsuperscript{7,72}

The adipocyte, as discussed previously, synthesises and releases TNF$\alpha$ which causes defects in insulin signaling leading to insulin resistance.\textsuperscript{29} Leptin regulates the intracellular utilization of fatty acids for energy, and therefore leptin resistance results in intracellular accumulation of triglycerides in skeletal muscle which decreases insulin-mediated glucose disposal. Reduced production of adiponectin in patients with obesity has also been associated with insulin resistance.\textsuperscript{73}

In obesity, the adipocytes release large amounts of NEFAs and it is thought that this may play a major role in insulin resistance. Indeed because of their excessive availability they will be used preferentially for energy production. Large amounts of NEFAs inhibit the action of insulin in peripheral tissues, and they also induce hepatic synthesis of clotting factors and can promote aggregation of platelets.\textsuperscript{74}

Fasting insulin level is an independent risk factor for CHD,\textsuperscript{75,76} and PAD is more prevalent in diabetic/impaired glucose tolerance subjects, compared to normal glucose tolerance subjects.\textsuperscript{72} Atherothrombotic complications in insulin resistance are partly attributed to the pro-thrombotic state including endothelial activation, hyperactivity of platelets, hypercoagulability and hypofibrinolysis.\textsuperscript{74} Plasma insulin levels
increase circulating PAI-1 levels, and show significant positive correlations with factor VII, fibrinogen and TF.\textsuperscript{75,76} Hyperglycaemia as previously mentioned can cause reactive oxygen species generation and oxidative stress.\textsuperscript{54}

The relationship between obesity, dyslipidaemia and thrombosis (Fig. 3)

Reduction of plasma HDL cholesterol is the most common lipid disturbance in obese subjects and is due in part to hypertriglyceridaemia, although low concentrations may often be seen without raised triglycerides in obese subjects.\textsuperscript{50} When present, hypertriglyceridaemia is accompanied by increases in small dense LDL, which is strongly atherogenic.\textsuperscript{50}

The high levels of NEFAs released in obesity, as well as inducing insulin resistance, are metabolised by the liver to increase hepatic synthesis of triglycerides and VLDL (very low density lipoprotein).\textsuperscript{50,54} High circulating levels of VLDL reduce HDL concentration and increase small dense LDL.\textsuperscript{12,54} Patients who lose weight show a decrease in serum LDL and triglyceride concentrations, and an increase in serum HDL concentrations.\textsuperscript{7}

Lipid disorders are also accompanied by platelet hyperactivity, hypercoagulability with increased factor VII, and hypofibrinolysis with increased PAI-1.\textsuperscript{78} High plasma levels of triglycerides increase oxidative stress by increasing production of superoxide. The increased flux of NEFAs from the adipocytes increases TF and PAI-1 levels and enhances platelet aggregation; all obviously promoting thrombosis.\textsuperscript{50} Lipoprotein(a) levels are raised in obesity, particularly when associated with hyperglycaemia. Lipoprotein(a) has LDL-like properties and is structurally similar to plasminogen. It therefore inhibits plasminogen binding to the endothelial cell and interferes with the generation of plasmin. Lipoprotein(a) levels are raised in patients with CHD and in those with intermittent claudication.\textsuperscript{79} Lipoprotein(a) is therefore both atherogenic and thrombogenic. Prothrombin levels and vitamin K-dependent coagulation factor levels are increased with hyperlipidaemia.\textsuperscript{38,41} High triglycerides and low HDL have also been associated with insulin resistance.\textsuperscript{75} HDL particles possess potent antioxidative activity and therefore oxidative stress is increased by the low HDL found with obesity.\textsuperscript{54}

Obesity and coronary thrombosis

Acute coronary syndromes (ACS) are usually triggered by rupture or erosion of an atheromatous plaque.\textsuperscript{51} When the plaque ruptures, endothelial TF is exposed to blood and activates the coagulation cascade causing thrombus formation.\textsuperscript{51} Obesity, acting through hyperlipidaemia and inflammation, may increase the vulnerability of the atherosclerotic plaque...

Fig. 3. Obesity, dyslipidaemia and thrombosis: how obesity and its effects on lipid metabolism may contribute to thrombosis.
Obesity and venous thromboembolism

Numerous studies have shown a clear relationship between obesity and the risk of idiopathic VTE (deep vein thrombosis [DVT] and pulmonary embolism [PE]), independent of other recognised risk factors (Odds Ratios [OR] of 2.26 and 2.42 in two separate studies comparing BMI $>$ 30 with BMI $<$ 25).5,6,81,82 Obese patients are also more likely to develop the post-thrombotic syndrome following DVT.83 The obese have chronically raised intra-abdominal pressure and decreased blood velocity in the common femoral vein.84 Inactivity, poor gait, as well as other life-style characteristics and co-morbidity, may further impair venous return from the lower limbs.

Obesity and stroke

Several large cohort studies have found a relationship between obesity and the risk of ischaemic stroke in men and in women (in three separate studies, an OR of 1.95 was found in men when BMI $>$ 30 was compared with BMI $<$ 23; an OR of 1.90 was found in women when BMI 29–32 was compared with BMI $<$ 21; and an OR of 3.0 was found when comparing the 4th quartile of WHR in men and women, with the 1st quartile).3,36,50,85–87 Increased risk of atherosclerosis, thrombotic potential and blood pressure are likely contributory factors. High leptin levels are associated with stroke (both haemorrhagic and ischaemic) independent of age and hypertension in both men and women.14

Obesity and peripheral arterial disease

There are few studies examining the relationship between obesity and PAD. Some cross-sectional and prospective cohort studies have found obesity to be a risk factor for development of PAD, whereas others have found an association to be lacking.88–90 It is suggested that this may be due to the higher prevalence of PAD in elderly males and in cigarette smokers; elderly males show a weaker relationship between obesity and cardiovascular disease, and smokers tend to have lower BMI than non-smokers.91 A recent cross-sectional study revealed a significant positive relationship between WHR and PAD prevalence, but not with BMI.92 Obese patients also have an increased prevalence of effort-related calf pain, which improves after weight loss; and patients with PAD are less likely to have progression of their disease, and more likely to have symptomatic improvement if they lose weight.88,93

Although the mechanisms by which obesity may cause PAD may be similar to CHD, the two disease states do have different risk profiles, for example, cigarette smoking is more strongly associated with development of PAD than CHD.94 Similarities are suggested by observations that high fibrinogen levels, increased markers of systemic oxidative stress, markers of impaired fibrinolysis, and increased inflammatory markers are also found in PAD.95–97 However, there remains a significant gap in our knowledge regarding the interrelationship of obesity and PAD, including aneurysms. Future studies should aim to ascertain the increased risk (if any) of developing PAD in obesity, particularly visceral obesity; the effect of obesity on complications of PAD, e.g. rupture of abdominal aortic aneurysm (AAA), critical limb ischaemia, requirement for major and minor limb amputations, and need for any interventions; the mechanisms by which obesity may cause PAD; and the benefits of weight reduction on preventing development of PAD, and progression of existing PAD. These areas should be addressed as a matter of urgency.

Conclusion

Obesity appears to be independently associated with both arterial and idiopathic venous thrombotic events. There are several mechanisms through which obesity can mediate its effects. The pro-thrombotic factors associated with obesity have been shown to improve with weight loss indicating that obesity is a modifiable risk factor for thrombosis.

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