Inflammation, Obesity, and the Metabolic Syndrome

Author J. S. Yudkin

Affiliation University College London, Gower Street, London WC1E 6BT, UK

Key words
- obesity
- insulin resistance
- adipocytokine
- tumour necrosis factor-α
- endothelium

Abstract

Adipose tissue expresses cytokines which inhibit insulin signalling pathways. Obesity also results in impairment of endothelium-dependent vasodilatation to insulin. We have previously suggested that adipocytokines might contribute to the coexistence of insulin resistance and endothelial dysfunction. However, the adipocytokine best characterised as causing insulin resistance is tumour necrosis factor-α (TNF-α), a molecule which under normal circumstances circulates in low concentrations. We propose a vasoregulatory role for local deposits of fat around blood vessels, which may contribute both to insulin action and to vascular endothelial dysfunction. In particular, we propose that the localised fat depot around the origin of skeletal muscle arterioles may play a physiological role in blood flow distribution. Isolated rat arterioles are under dual regulation by insulin, which activates both endothelin-1 mediated vasoconstriction and nitric oxide mediated vasodilatation. In obese rat arterioles, insulin-stimulated nitric oxide synthesis is impaired, resulting in unopposed vasoconstriction. We propose this to be the consequence of production of TNF-α from the fat surrounding the vessel origin – a depot to which we ascribe a specialist vasoregulatory role. We suggest that this cytokine accesses the nutritive vascular tree to inhibit insulin-mediated capillary recruitment – a mechanism we term 'vasocrine' signalling. We also suggest a homology between periarteriolar fat and both periarterial and visceral fat, which may, through outside-to-inside signalling, play a direct role in producing the inflammatory changes found in atherosclerotic plaques, so explaining relationships between visceral fat, insulin resistance, and vascular disease.

received 16.10.2006
accepted 18.01.2007

Bibliography
DOI 10.1055/s-2007-985898
Horm Metab Res 2007; 39: 707–709
© Georg Thieme Verlag KG Stuttgart · New York
ISSN 0018-5043

Correspondence
Prof. J. S. Yudkin, MD, FRCP
Emeritus Professor of Medicine
University College London
28, Huddleston Road
London
London N7 OAG
UK
Tel.: +44/20/7607 38 55
Fax: +44/20/7607 25 06
j.yudkin@ucl.ac.uk

The clustering of dyslipidaemia, hypertension, and glucose intolerance has been recognised for 4 decades. However, the Metabolic Syndrome gained publicity and prominence following Reaven's Lilly Lecture in 1988 [1]. Since that time, the number of component features has expanded to include other lipid disturbances, elevated levels of proinsulin, and abnormalities of coagulation and fibriolysis. More recently, several other features have been described in this cluster, including markers of low grade inflammation (such as C-reactive protein), microalbuminuria, and endothelial dysfunction. And it is these characteristics which, perhaps unlike hypertension and dyslipidaemia, challenge the tenet that the central aetiological factor in the cluster is insulin resistance.

We have shown, using a technique of Z scores, that in 107 healthy subjects, there are close correlations between 8 metabolic syndrome variables and 4 of acute phase activation [2]. Furthermore, the acute phase score correlated with that of 7 markers of endothelial activation. In such a model, there was no residual relationship of the metabolic syndrome score and the endothelial score. These findings suggest that low grade inflammation might underlie both the clustering of the Metabolic Syndrome, including the presence of insulin resistance, and its relationship with vascular damage. There are, moreover, strong biological grounds for these epidemiological observations. In a recent paper, mice in which constitutively active IKK-β was expressed in hepatocytes, producing overexpression of liver NFκB, showed insulin resistance both in liver and skeletal muscle [3], implying the existence of a signal originating from the 'inflamed' liver.

These observations raise the question as to the origin of the low grade inflammatory state in

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

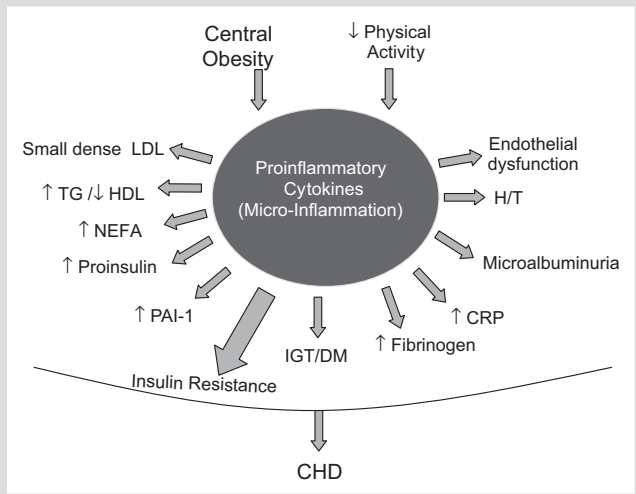

Fig. 1 The role of central obesity and adipocytokines in the clustering of 'Metabolic Syndrome' risk factors.
LDL: low density lipoprotein; TG: triglycerides; HDL: high density lipoprotein; NEFA: nonesterified fatty acids; PAI-1: plasminogen activator inhibitor-1; IGT: impaired glucose tolerance; DM: diabetes mellitus; CRP: C-reactive protein; H/T: hypertension; CHD: coronary heart disease.
Based on figure in: Yudkin JS. Insulin resistance and the Metabolic Syndrome – on the pitfalls of epidemiology. Diabetologia 2007; 50: 1576-1586: With kind permission of Springer Science and Business Media.

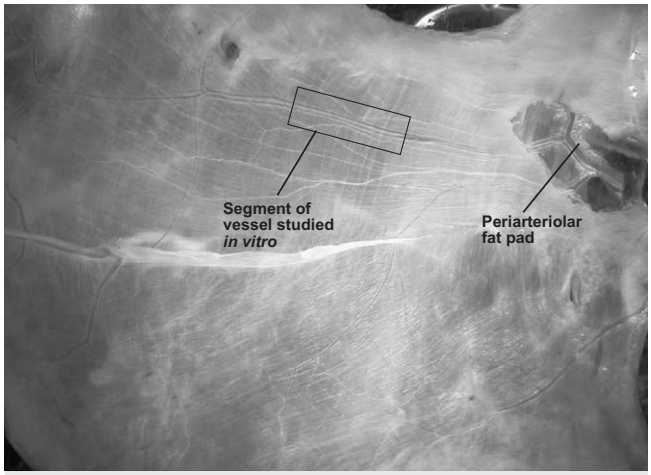

Fig. 2 Isolated cremaster muscle from Zucker fatty rat*.
*Reprinted from: Yudkin JS, Eringa E, Stehouwer CDA. The Lancet 2005; 365: 1817–1820. Vasocrine signalling from perivascular fat – a mechanism linking insulin resistance and vascular disease; Copyright (2005), with permission from Elsevier.

these healthy subjects. We explored the possibility of chronic infection with Helicobacter, Chlamydia, or cytomegalovirus, but relationships between antibody titres and inflammatory markers were weak. Much stronger were the correlations between measures of obesity, particularly central fat, and those of acute phase proteins [2]. In these subjects around 15–20% of the variance of the acute phase score was statistically dependent upon obesity. This led to our proposing the hypothesis that the generation of an inflammatory signal from adipose tissue underlay the clustering of metabolic syndrome variables, including insulin resistance, with endothelial dysfunction, and perhaps vascular disease (**Fig. 1**).

This now raises a new dilemma: how do the liver, and skeletal muscle, and blood vessels know that one is fat? The likelihood is that fat mass signals to distant tissues and organs via the medium of a circulating signalling molecule. Nonesterified fatty acids may well play such a role, but more recently substantial interest has focused on the potential role of adipocytokines. Indeed the release of fatty acids may be dependent on the degree of low grade inflammation in the adipose tissue. A number of potential candidate adipocytokines may induce muscle and liver insulin resistance, including interleukin-6 (IL-6), resistin, leptin, retinol binding protein-4 [4], and (inversely) adiponectin. However, the cytokine which has been best characterized as downregulating the insulin signalling pathway, and also producing endothelial activation, is tumour necrosis factor-α (TNF-α). Yet we have found no net release of TNF-α from an adipose issue bed [5], suggesting that, other than in severe inflammatory illness, it is unlikely to play a major endocrine role.

It has been recognised that in conditions of calorie excess, fat accumulation occurs both in hepatocytes and in skeletal muscle fibres, and this may play a major role in insulin resistance in these tissues. Obese subjects show endothelial dysfunction, including resistance to insulin-mediated vasodilatation, so implying vascular insulin resistance. Indeed it has been suggested that this component part of insulin resistance may impede the ability of the hormone to augment its delivery, and that of substrate, to skeletal muscle in the postprandial state [6]. Such action may not require an increase in total limb blood flow, but might represent the diversion of flow from non-nutritive to nutritive circuits, something of which insulin is capable in a short timeframe and in low physiological concentrations [7].

With colleagues in Amsterdam, we have been exploring insulin's effect on the vasculature, using a model of an *ex vivo* first order arteriole isolated from a rat cremaster muscle [8]. The vessel is cannulated and maintained at 60 mmHg in an organ bath, where it is exposed to vasoactive substances. Using an arteriole from a lean rat, insulin has no net effect on vessel diameter, but with the use of inhibitors of insulin signalling pathways, this can be shown to represent equivalent degrees of vasodilatation – mediated through the PI-3 kinase pathway and with nitric oxide as the vasodilator – and vasoconstriction – mediated by endothelin-1 via the ERK pathway. If a similar experiment is done using a similar arteriole isolated from an obese Zucker rat, incubation with insulin produces vasoconstriction, which is inhibited by an endothelin-1 receptor blocker. The combination of insulin and the endothelin-1 inhibitor in the obese vessel produces no net change in diameter, but the same combination in the vessel from the lean rat produces net vasodilatation. These observations show that in the vessel from the obese rat, the PI3-kinase pathway of insulin action is impaired, leaving unopposed insulin stimulated ERK-pathway vasoconstriction, mediated by endothelin-1.

Further studies comparing the arterioles of lean with those of obese rats have shown a reduction in the expression of endothelial nitric oxide synthase in the endothelial cells from the obese vessels. The inhibition of PI3-kinase-mediated insulin signalling, of nitric oxide synthase expression, and thus of insulin-mediated vasodilatation are known consequences of the action of TNF-α [9, 10], and we have found that incubating the cremaster arteriole of lean rats with insulin in combination with TNF-α produces similar effects to those of obesity [8], producing vasoconstriction which can be overcome by an endothelin-1 receptor blocker. This raises the possibility that adipocytokines such as TNF-α are secreted from fat depots, either remote from or in close proximity, to the vessels. Yet as pointed out above, adipose tissue does not appear to secrete this cytokine in substantial amounts, and circulating TNF-α is bound to excess

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

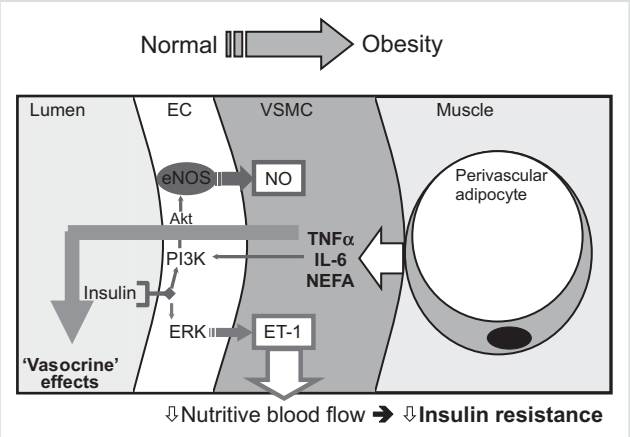

Fig. 3 Vasocrine signalling from perivascular fat*.
Adipocytokines secreted from perivascular adipocytes inhibit the PI3-kinase pathway of insulin signalling, leaving unopposed vasoconstrictor effects of endothelin-1. High concentrations of tumour necrosis factor-α access the vascular lumen, resulting in inhibition of endothelial PI3-kinase pathway insulin signalling in downstream vessels. Reduced insulin-mediated enhancement of muscle nutritive blood flow will contribute to insulin resistance. EC: endothelial cell; VSMC: vascular smooth muscle cell; eNOS: endothelial nitric oxide synthase; NO: nitric oxide; PI3-K: phosphoinositol-3-kinase; TNF-α: tumour necrosis factor-α; IL-6: interleukin-6; NEFA: nonesterified fatty acids; ERK: extracellular signal-related kinase; ET-1: endothelin-1. *Reprinted from: Yudkin JS, Eringa E, Stehouwer CDA. The Lancet 2005; 365: 1817–1820. Vasocrine signalling from perivascular fat – a mechanism linking insulin resistance and vascular disease; Copyright (2005), with permission from Elsevier.

amounts of the specific binding proteins [11], both of which factors make it improbable that TNF-α acts as a systemic circulating signal. We have proposed a novel mechanism to explain these observations [8]. The morphology of the rat cremaster muscle arteriole differs between lean and obese animals, in that there is a circumscribed depot of fat only around the origin of the vessel in the obese rat (**Fig. 2**). We have suggested that this may provide a regulatory mechanism whereby, in situations of calorie excess or inactivity, a local fat pad develops at the vessel origin with specialist vasoregulatory function. Adipocytokines from these pads, such as TNF-α, inhibit the PI3-kinase signalling pathway of endothelial NO production, thus locally inhibiting a systemic postprandial insulin-mediated vasodilatation and helping the organism to protect its muscle from substrate over-supply.

It must be noted, however, that the localization of the fat pad in the arteriole from the Zucker rat is proximal to the segment of vessel which shows altered insulin signalling. For this reason, we have proposed a mechanism to explain the propagation of the signalling function of TNF-α. It is suggested that the increased endothelial permeability, consequent upon the cytokine's action, allows it to access the circulation, where it locally exceeds the binding capacity of circulating binding proteins, so producing inhibition of insulin-mediated vasodilatation throughout the entire nutritive vascular tree. We have used the term "vasocrine signalling" to define this proposed signalling mechanism [8].

Our hypothesis is shown diagrammatically in **Fig. 3**. The vascular smooth muscle cell in nutritive arterioles is under dual regulation by insulin. Under normal circumstances, postprandial insulin secretion will cause a predominantly vasodilatory response, mediated by endothelially derived nitric oxide, with a consequent increase in supply of substrate and hormone to skeletal muscle. However, in circumstances of calorie excess, the accumulation of periarteriolar fat generates production of adipocytokines, which block the vasodilatory response and instead may even produce vasoconstriction. Such action throughout the nutritional vascular bed could contribute to muscle insulin resistance.

Depots of adipose tissue are found around large vessels as well as small. It is proposed that there is a homology between such perivascular depots, which secrete substantial amounts of adipocytokines such as TNF-α, and that this is responsible for outside-to-inside signalling, in arteries as in arterioles. We postulate that in conditions of inactivity and calorie excess, such depots around the coronary, carotid, and femoral arteries may contribute to inflammatory changes, and so to atherothrombosis, in the affected arteries [12]. It is noted that there are close relationships between measures of epicardial and those of visceral fat [13], and the predictive power of waist, and perhaps neck, circumference for coronary heart disease may relate to more direct influences of the adipose depot on the vessels than those mediated by circulating signals – be they nonesterified fatty acids, insulin or adipocytokines. These speculations, however, remain as hypotheses, as a detailed characterisation of perivascular fat, and its physiological and pathophysiological role, remains to be elucidated.

References

1 *Reaven GM*. Role of insulin resistance in human disease 1988. Banting Lecture. Diabetes 1988; 37: 1595–1607
2 *Yudkin JS, Stehouwer CDA, Emeis JJ, Coppack SW*. C-reactive protein in healthy subjects: association with obesity, insulin resistance, and endothelial dysfunction. Arterioscleros Thromb Vasc Biol 1999; 19: 972–978
3 *Cai D, Yuan M, Frantz DF, Melandez PA, Hansen L, Lee J, Shoelson SE*. Local and systemic insulin resistance resulting from hepatic activation of IKK-beta and NF-kappaB. Nature Medicine 2005; 11: 183–190
4 *Yang O, Graham TE, Mody N, Preitner F, Peroni OD, Zabolotny JM, Kotani K, Quadro L, Kahn BB*. Serum retinol binding protein 4 contributes to insulin resistance in obesity and type 2 diabetes. Nature 2005; 436: 356–362
5 *Mohamed-Ali V, Goodrick S, Rawesh A, Katz D, Miles JM, Katz DR, Yudkin JS, Coppack SW*. Subcutaneous adipose tissue secretes interleukin-6 but not tumour necrosis factor-α in vivo. J Clin Endo Metab 1997; 82: 4196–4200
6 *Baron AD, Steinberg HO, Chaker H, Leaming R, Johnson A, Brechtel G*. Insulin-mediated skeletal muscle vasodilation contributes to both insulin sensitivity and responsiveness in lean humans. J Clin Invest 1995; 96: 786–792
7 *Zhang L, Vincent MA, Richards SM, Clerk LH, Rattigan S, Clark MG, Barrett EJ*. Insulin sensitivity of muscle capillary recruitment in vivo. Diabetes 2004; 53: 447–453
8 *Yudkin JS, Eringa E, Stehouwer CDA*. Vasocrine signalling from perivascular fat - a mechanism linking insulin resistance and vascular disease. Lancet 2005; 365: 1817–1820
9 *Mohamed F, Monge JC, Gordon A, Cernacek P, Blais D, Stewart DJ*. Lack of role for nitric oxide (NO) in the selective destabilisation of endothelial NO synthase mRNA by tumor necrosis factor-alpha. Arterioscler Thromb Vasc Biol 1995; 15: 52–57
10 *Zhang L, Wheatley CM, Richards SM, Barrett EJ, Clark MG, Rattigan S*. TNF-alpha acutely inhibits vascular effects of physiological but not high insulin or contraction. Am J Physiol Endocrinol Metab 2003; 285: E654–E660
11 *Hotamisligil GS, Spiegelman BM*. Tumor necrosis factor alpha: a key component of the obesity-diabetes link. Diabetes 1994; 43: 1271–1278
12 *Mazurek T, Zhang LF, Zalewski A, Mannion JD, Diehl JT, Arafat H, Sarov-Blat L, O'Brien S, Keiper EA, Johnson AG, Martin J, Goldstein BJ, Shi Y*. Human epicardial adipose tissue is a source of inflammatory mediators. Circulation 2003; 108: 2460–2466
13 *Iacobellis G, Ribaudo MC, Assael F, Vecci E, Tiberti C, Zappaterreno A, Di Mario U, Leonetti F*. Echocardiographic epicardial adipose tissue is related to anthropometric and clinical parameters of metabolic syndrome: a new indicator of cardiovascular risk. J Clin Endo Metab 2003; 88: 5163–5168

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.