Obesity and diabetes

KONSTANTINOS LOIS AND SUDHESH KUMAR

Warwickshire Institute of Diabetes, Endocrinology & Metabolism (WISDEM). University Hospital Coventry & Warwickshire. Warwick Medical School Coventry. UK.

Obesity and diabetes are closely linked to each other and are causatively associated with an atherogenic milieu that increases the risk of adverse cardiovascular events and mortality from all causes. The scope of this article is to describe the most widely accepted theories that link the two diseases, cast light on the unifying metabolic defect and highlight the current and future therapeutic management.

INTRODUCTION

Obesity is a serious growing global health problem affecting more than 400 million people worldwide. It is associated with more than 45 comorbidities and a cluster of atherogenic disorders that compose the metabolic syndrome; the later is recognized by the International Diabetes Federation guidelines as a progressive condition that contributes to the development of diabetes, increases the risk of adverse cardiovascular events and the mortality from all causes. Although intensively researched, a clear answer to why some people are obese and some lean has not been given yet. Analysis of wealth of data support the interaction between genetic, cultural and environmental-behavioral factors with relative impact accounted for 30%, 10% and 60%, respectively as underlying causes of obesity[1]. The resultant imbalance between energy intake and expenditure results eventually in excess energy storage in the form of fat.

The prevalence of diabetes has also taken a sharp and unexpected upward turn the late few years. Large epidemiologic studies reveal the parallel escalation of the obesity and diabetes epidemics. Both these metabolic disorders are characterized by defects of insulin action; the term 'diabesity' express their close relationship to each other. Up to date, several theories linking different pathogenic mechanisms that make obese individuals resistant to insulin and their pancreatic β-cells to fail leading eventually to frank diabetes have been suggested. A unifying hypothesis however, still remains elusive.

POTENTIAL MECHANISMS LINKING OBESITY TO DIABETES

Most of the suggested theories that link obesity to diabetes recognize insulin resistance (IR) as the unifying metabolic defect that

Correspondence: Prof. S. Kumar.
Warwickshire Institute of Diabetes, Endocrinology & Metabolism (WISDEM).
University Hospital Coventry & Warwickshire.
Warwick Medical School Coventry. UK.
E-mail: Sudhesh.Kumar@warwick.ac.uk

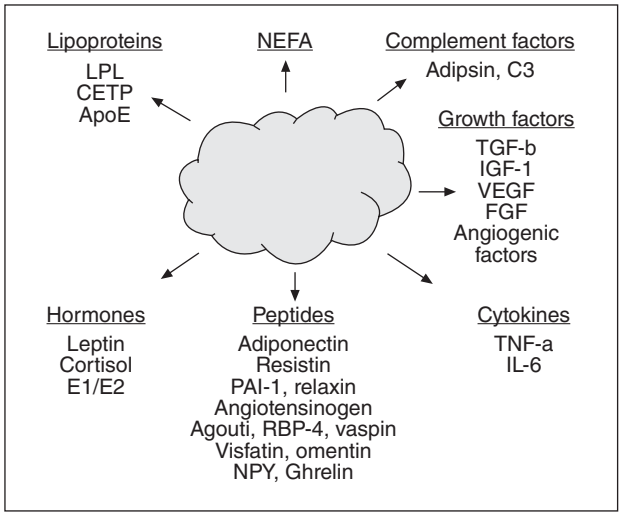

Fig 1. Cytokines, chemokines, acute phase proteins and other inflammation-related proteins secreted from adipose tissue.

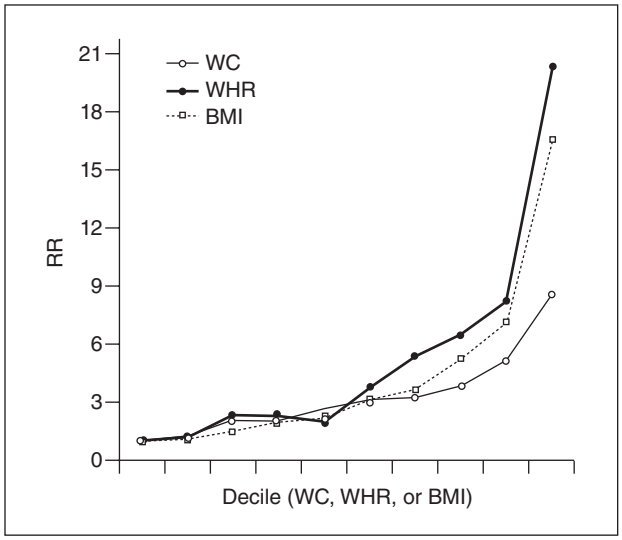

Fig. 2. Age-adjusted relative risk (RR) of type 2 diabetes by baseline waist circumference (WC), waist-to-hip ratio (WHR), and body mass index (BMI) deciles[19].

links obesity to diabetes (fig. 1). Vague et al first in 1956 identified the heterogeneity of obesity with respect to regional distribution and biological properties of fat tissue[2]. Kissebah and Krakower in 1994[3] and later on many other researchers showed that central adiposity represents an independent risk factor for the development of IR and diabetes later in life (fig. 2).

"Randle's glucose-fatty acid" hypothesis

For many years, the views on metabolic derangements of diabetes have been largely "glucocentric", considering hyperglycemia the main underlying cause. Philip Randle however in 1963 proposed one set of metabolic pathways by which carbohydrate and fat metabolism interact[4]. The so called "Randle's cycle" provides the reciprocal relationship between fatty acid oxidation and glucose oxidation, according to which the enhanced non-esterified fatty acid (NEFA) oxidation inhibits glucose metabolism. Thus, in body situations with lipid excess, as in obesity, the increased plasma NEFAs augment by mass action their cellular uptake and induce their mitochondrial β-oxidation, blocking at the level of substrate competition, intermediates accumulation, enzyme regulation, intracellular signaling and/or gene transcription the glucose metabolism. Clinical studies in healthy volunteers with acute elevation of plasma NEFAs resulted in whole body IR, confirming the proposed metabolic model[5]. Source of the NEFA excess in obese individuals are considered the meal-derived fatty acids and lipolysis of the adipose tissue. The visceral fat in particular is of considerable significance in the NEFA flux to the liver as according to Frayn[6] in obese individuals the omental fat fails to switch from a negative to a positive NEFA balance during the transition from fasting to the postprandial state resulting in enhanced NEFAs mobilization even postprandially. Furthermore, in comparison to the peripheral-gluteal adipose tissue, central-abdominal fat is metabolically and lipolytically more active, releasing more NEFAs in the bloodstream[7]; regional differences in the number and sensitivity of adrenoreceptors[8], the activity of 11β-HSD1[9] and the response of adipocytes to lipogenic/anti-lipolytic effects of insulin are considered the underlying pathogenic mechanisms.

Ectopic fat storage hypothesis

Although until recently, adipose tissue was considered the only tissue in the human body that stores fat, Ravussin et al[10] showed that when the diet-derived fat intake is increased, fat storage within and around other tissues and organs including liver, skeletal muscle and pancreatic β-cells, which under normal conditions do not store lipids, takes place. This in turn results in excessive mitochondrial production of toxic reactive lipid species that cause organ-specific oxidative damage and cellular dysfunction, leading progressively to the development of IR, impaired glucose metabolism and finally to diabetes (Ectopic fat storage hypothesis)[11]. The accumulation of toxic metabolites within the pancreatic islet β-cells in particular affects insulin secretion and enhances β-cell apoptosis accelerating the progression to overt diabetes.

Oxidative stress

Oxidative stress refers to a condition in which imbalance between oxidant generation and antioxidant protection or repair of oxidative damage exists. Normally, during the aerobic cellular metabolic processes, seve-

ral reactive oxygen species (ROS) are produced which act as necessary messengers in biological systems (Redox signaling). A currently favored hypothesis sets oxidative stress as the common pathogenic factor leading to IR, β-cell dysfunction, impaired glucose tolerance and eventually to diabetes in obese individuals. The supporters of this theory suggest that the peroxisomal, β-oxidation of NEFA excess, leads to excessive intracellular ROS production which in turn activate multiple stress-sensitive signaling cascades that eventually inactivate insulin receptor and inhibit insulin action. In β-cells, which seem to be very sensitive to oxidative stress due to deficiency in antioxidant enzymes, the accumulating free radicals damage the mitochondria and thus blunt the glucose-induced insulin secretion and enhance the cellular apoptosis.

The role of adipose tissue as an endocrine organ

The recognition of humoral and neuronal cross-talk between adipocytes, as well as between adipose tissue and distant organs via various receptors that are expressed in the fat tissue and of a vast array of adipocyte-derived bioactive factors (adipocytokines) with local and systemic effects changed the previous consideration of fat tissue as inert storage depot (table 1). Adipose tissue is nowadays considered a very active endocrine organ which seems to play an essential role in the regulation of whole body's metabolism and energy homeostasis[12]. It is suggested that altered secretion of adipocytokines by the extremely enlarged adipocytes in obesity, profoundly affects insulin sensitivity and might potentially link obesity with diabetes. The increased plasma resistin along with the decreased concentration of adiponectin is compatible with this suggestion.

Further to its role as endocrine organ that produces bioactive agents which affect whole body's metabolism, studies have also proven that adipose tissue modifies the metabolism of circulating hormones. The well defined increased concentration of glucocorticoids in the visceral fat tissue of obese individuals provides another mechanism of the detrimental effects of central obesity on glucose metabolism, as glucocorticoids antagonize insulin effects. The enhanced expressions of 11β-HSD1 within the visceral fat tissue[9] as well as the increasing expression of 5-alpha reductase type 1 with increasing obesity[13] provide the biochemical background of the persistently elevated glucocorticoid effect in obese individuals.

Obesity as a low-grade inflammatory state

In the last decade, scientists have come to view obesity as a low-grade inflammatory state. The increased plasma circulating mononuclear cells and lymphocytes in obese individuals, as well as the adipose tissue and whole body's increased concentration of C-reactive protein (CRP), tumour necrosis factor (TNF)-α, interleukin (IL)-1 and IL-6 are compatible with this suggestion. Adipose tissue per se is considered the initial site of the pro-inflammatory state generation which eventually expands to the whole body. Visceral fat appears to produce pro-inflammatory markers more actively than subcutaneous adipose tissue, confirming the crucial role of central obesity in the pathogenesis of the obesity-associated morbidities (fig. 3). The suggested pathogenic mechanism involves several heterogeneous factors in the generation of inflammation within the adipose tissue including tissue hypoxia, toxic effects of the excessive fat storage, gut derived

TABLE 1. Differences between adipocytes from subcutaneous (Sc) and visceral depots[18]

Factor	Regional difference	Reference
Leptin mRNA and protein	Visceral < Sc	Lefebvre et al, 1998; Montague et al, 1997; Harmalen et al, 1998
TNF-α	Visceral < Sc	Hube et al, 1999
IL-6	Visceral > Sc	Fried et al, 1998
PAI-1	Visceral > Sc	Shimomura et al, 1996
Angiotensinogen mRNA	Visceral > Sc	Van Harmalen et al, 2000
Resistin	Visceral = Sc	McTernan et al, 2002a
Adiponectin	Visceral < Sc	Fisher et al, 2002
Androgen receptor mRNA	Visceral > Sc	Dieudonne et al, 1998
PPARγ	visceral = Sc	Montague et al, 1998
TZD stimulated pre-adipocyte differentiation	Visceral < Sc	Adams et al, 1997
Lipolytic response to catecholamines	Visceral > Sc	Rebuffé-Scrive M et al, 1989
Antilipolytic effect of insulin	Visceral < Sc	Zierath et al, 1998 Lefebvre et al, 1998
β1 and β2-Adrenergic receptor binding and mRNA	Visceral > Sc	Hellmér et al, 1992; Arner et al, 1990
Dexamethasone-induced increase in LPL	Visceral > Sc	Fried et al, 1993
α2-Adrenergic receptor agonist inhibition of cAMP	Visceral < Sc	Vikman et al, 1996
Insulin receptor affinity	Visceral < Sc	Zierath et al, 1998
IRS-1 protein expression	Visceral < Sc	Zierath et al, 1998
Insulin receptor (exon 11 deleted)	Visceral > Sc	Lefebvre et al, 1998
Glucocorticoid receptor mRNA	Visceral > Sc	Rebuffé-Scrive et al, 1990

IL: interleukin; TNF: tumour necrosis factor.

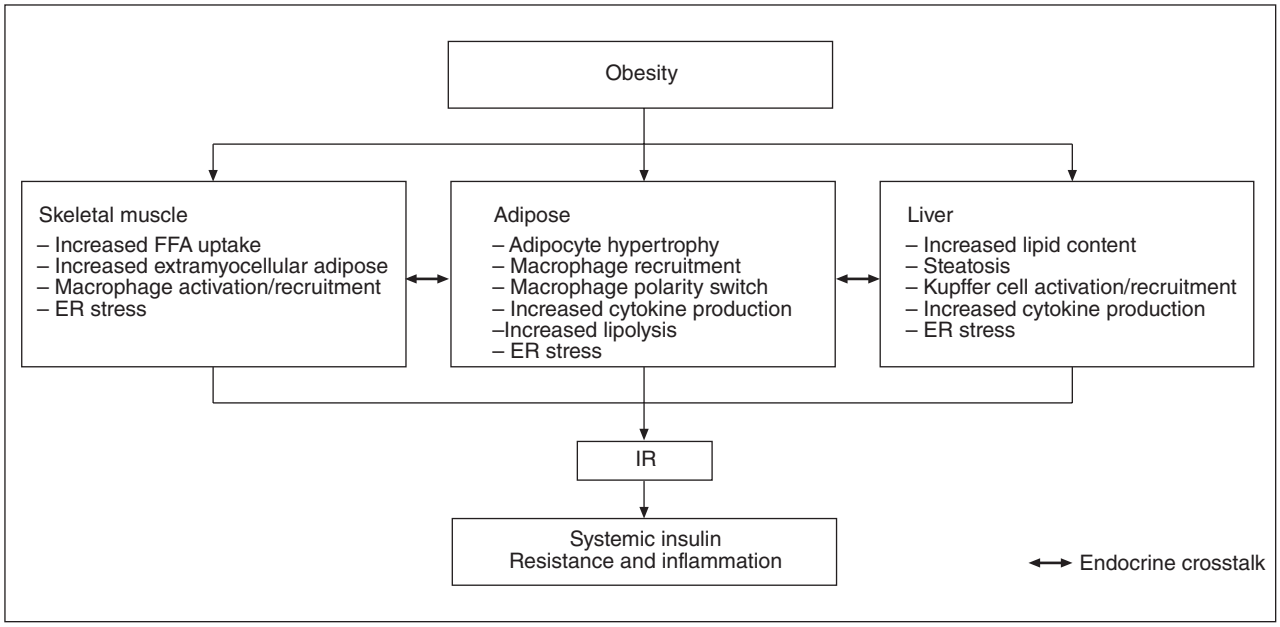

Fig. 3. Role of obesity in inflammation-dependent insulin resistance[20]. ER: endoplasmic reticulum; IR: insulin resistance.

pathogen-associated molecular patterns (PAMPs), macrophages infiltration and increased adipocytes necrosis. An overlap between metabolic and inflammatory signaling pathways that impair insulin effect in peripheral tissues has been demonstrated[14,15] linking the obesity-related pro-inflammatory state to IR and diabetes. Meanwhile the local, within the fat tissue inflammation affects the adipocytes which become less insulin sensitive; the resultant suppressed pre-adipocytes differentiation and the increased NEFA efflux to the bloodstream enhances the ectopic fat storage and affects peripheral glucose metabolism. Initially, the adipocytes have been exclusively blamed for the fat tissue-derived pro-inflammatory cytokines[16]. Recent studies however[17] revealed that obesity is associated with increased infiltration of adipose tissue with macrophages which also secrete in high concentrations inflammatory bioactive agents that fuel systemic inflammation.

Therapies targeting adipose tissue and insulin resistance

Strategies that reduce fat mass are the cornerstone for the prevention, amelioration and treatment of obesity and the associated IR. Increased physical activity and healthy diet with controlled calorie intake remain the first line treatment, while anti-obesity drugs (orlistat, siutramine) and bariatric surgery work additionally to lifestyle changes for loss of the excessive body weight.

In current clinical practice drugs such as metformin and PPAR-γ agonists as well as glucagon-like peptide (GLP)-1 analogues and dipeptidylpeptidase (DPP)-4 inhibitors are the main pharmaceutical interventions for the treatment of established IR. Several novel medications that target specific molecules and biochemical pathways implicated in the pathogenesis of IR including INT131 besylate, metaglidasen and MBX-2044, as well as 11β-HSD1 inhibitors (arylsulfonamidothiazole and adamantyltriazoles), glucocorticoid receptor inhibitors and factors that reverse endoplasmic reticulum stress and restore its function (salubrinal, 4-Phenyl butyric acid and taurine-conjugated ursodeoxycholic acid) promise more effective treatment of IR in the future. The late few years the administration of nutritional supplements (e.g. chromium, magnesium, vitamin D) and pre-/pro-biotics that alter gut flora to 'lean' type for the amelioration of IR and diabetes gains many supporters. Similarly do the centrally acting insulin sensitizers including leptin and dopamine D2 receptor agonists. Their role however in clinical practice remains to be proved.

CONCLUSION

Obesity and the associated IR are causatively related to an atherogenic metabolic milieu that increases the cardiovascular risk and mortality from all causes making the need of effective treatment more than imperative. Although several drugs with anti-obesity properties and insulin sensitizing effects are currently used in clinical practice and much more will come on the market the following few years, the clinical practitioners should keep in mind that prevention is always better than treatment. Thus, the importance of healthy lifestyle in preventing the development of metabolic disor-

ders should be emphasized and more intensive actions for the information of the public should be taken by the medical community and authorities.

Conflict of interest

The authors declare they have no conflict of interest.

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