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Fatty acids and the metabolic syndrome

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The metabolic syndrome is a very common condition, characterised by insulin resistance, dyslipidaemia, abdominal obesity and hypertension, that is associated with a high risk of type 2 diabetes mellitus (T2DM) and CVD. Obesity is a key aetiological factor in the development of the metabolic syndrome. In light of the increasing prevalence of obesity, there is a high requirement to reduce the impact of the adverse health effects associated with the metabolic syndrome. The aetiological role of nutrient-derived metabolic stressors, in particular fatty acids, in the development of obesity and the metabolic syndrome is explored. Also, the evidence that pro-inflammatory stressors may predispose to obesity-induced insulin resistance is reviewed. The present paper explores the concept that reducing the impact of metabolic and inflammatory stressors may reduce the adverse health effects of obesity and slow the progression towards the metabolic syndrome and T2DM. Evidence from human dietary intervention studies that have investigated the potential therapeutic effects of dietary fatty acid modification is explored. The present review highlights the requirement to take account of genetic background, within the context of nutrient regulation of gene expression and individual responsiveness to dietary therapy. This approach will further the understanding of the interaction between fatty acids in the pathogenesis and progression of the metabolic syndrome.

Metabolic syndrome: Fatty acids: Gene expression: Insulin resistance: Inflammation: SREPB-1c

The metabolic syndrome

The metabolic syndrome represents a multi-component disorder that is characterised by impaired insulin sensitivity, dyslipidaemia, abdominal obesity and hypertension. It is associated with a high risk of subsequent development of type 2 diabetes mellitus (T2DM), CVD and premature death (Isomaa *et al*. 2001). The WHO have defined the metabolic syndrome as impaired insulin sensitivity, glucose intolerance or diabetes mellitus in combination with at least two other metabolic derangements, including abdominal obesity, dyslipidaemia (increased triacylglycerol (TAG) or reduced HDL-cholesterol concentrations) and urinary microalbuminuria (Alberti & Zimmet, 1998). The National Cholesterol Education Program Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) (2001) have proposed that individuals with the metabolic syndrome have three or more of the five criteria listed in Table 1.

Obesity has been identified as the key aetiological condition that predisposes to the development of the metabolic syndrome (Kahn & Flier, 2000). Given the increasing prevalence of obesity, there is a high requirement to reduce the impact of the adverse health effects, particularly T2DM and CVD. By 2010, approximately thirty-one million of the population in Europe and an estimated 239 million worldwide will require treatment for T2DM and its related complications (King *et al*. 1998; Zimmet *et al*. 2001). The link between obesity and T2DM is because of adverse effects of excess body fat on systemic responsiveness to insulin, resulting in impaired action of insulin for both carbohydrate and lipid metabolism, which leads to a compensatory hyperinsulinaemia (Saltiel, 2000). Insulin resistance is the central metabolic perturbation of the metabolic syndrome and T2DM. Fig. 1 illustrates the potential pathway between obesity and insulin resistance, towards the metabolic syndrome and T2DM. This pathway represents a progressive phenotype. Insulin resistance

Abbreviations: CLA, conjugated linoleic acid; IR, insulin receptor; SFA, saturated fatty acids; SREBP, sterol regulatory element-binding protein; T2DM, type 2 diabetes mellitus; TAG, triacylglycerols.

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Table 1. The National Cholesterol Education Program Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) (2001) criteria for the metabolic syndrome

Waist girth (mm)	
Men	>1020
Women	>880
HDL-cholesterol (mmol/l)	
Men	<1·1
Women	<1·3
Triacylglycerol (mmol/l)	>1·7
Blood pressure (mm Hg)	130/85
Fasting blood glucose (mmol/l)	>6·1

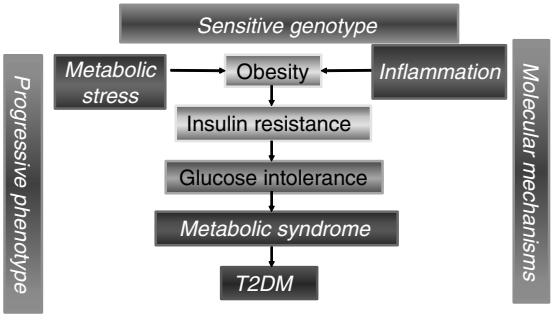

Fig. 1. The development and progression of the metabolic syndrome. T2DM, type 2 diabetes mellitus.

is a relatively common pathological state, whereby target tissues fail to respond effectively to normal circulating concentrations of insulin and reduced glucose transport in muscle and adipose tissue (Le Marchand-Brustel *et al*. 2003). Pancreatic β-cells first compensate for peripheral insulin resistance by increasing basal and postprandial insulin secretion to maintain euglycaemia. At some point β-cells fail to respond effectively and there is deterioration of glucose homeostasis, which leads to the development of glucose intolerance. Impaired insulin action and hyperinsulinaemia lead to a variety of abnormalities in liver, muscle and adipose tissue that result in elevated NEFA and TAG concentrations, low HDL levels, hyperglycaemia, impaired glucose disposal, a prothrombotic state and increased vascular resistance (Saltiel, 2000). Hypothetically, individuals with a sensitive genotype will be most susceptible to the impact of metabolic and pro-inflammatory stressors. The present paper will explore the hypothesis that the interaction between metabolic stressors and inflammation, particularly in adipose tissue, are key initiators of insulin resistance.

Several lines of evidence suggest that both metabolic stressors (e.g. NEFA) and pro-inflammatory signals (e.g. TNF-α) induce insulin resistance by inhibiting insulin signalling (Zick, 2001). Animal studies suggest that it may be possible to attenuate the interaction between metabolic and inflammatory stressors to improve insulin sensitivity. For example, lipid infusion fails to induce insulin resistance in skeletal muscle of IκB kinase β-knock-out mice and salicylate treatment prevents fat-induced muscle insulin resistance by inhibiting IκB kinase β activity (Kim *et al*. 2001). A greater understanding of the molecular mechanisms that underlie this progressive disease needs to be defined, so that evidence-based nutritional therapies can be developed to attenuate the impact of obesity-induced insulin resistance. The present paper will explore the concept that the potential impact of obesity may be attenuated by reducing the impact of metabolic and inflammation stressors to slow the progression towards the metabolic syndrome and T2DM. A notable development is recent evidence from controlled trials that shows that both diet and exercise are effective in preventing the development of T2DM in high-risk individuals (Knowler *et al*. 2002; Mann, 2002).

Adipose tissue and insulin resistance

There are at least two ways whereby adipose tissue may influence glucose homeostasis and act as the key aetiological factor in the development of insulin resistance and the metabolic syndrome (Kahn & Flier, 2000). First, excessive adipose tissue energy storage results in increased fatty acid flux to other tissues and increased TAG storage in peripheral tissues, which promotes insulin resistance. Second, adipose tissue is an important endocrine organ that secretes several inflammatory factors, collectively known as adipocytokines or adipokines, which have a direct effect on insulin sensitivity. The present paper will focus on the pro-inflammatory component of insulin resistance and show how dietary fatty acids may reduce the impact of these cellular stressors. The important adipocytokines include TNF-α, leptin, plasminogen activator protein-1, IL-6, resistin, angiotensin and adiponectin (also known as Acrp-30) (Dandona *et al*. 2004). The insulin-desensitising effects of TNF-α are probably the best characterised. TNF-α inhibits autophosphorylation of tyrosine residues of the insulin receptor (IR), promotes serine phosphorylation of insulin receptor substrate-1, which in turn causes serine phosphorylation of IR in adipocytes, and inhibits tyrosine kinase phosphorylation (Hotamisigil, 2003); the combined effects ultimately lead to insulin resistance and glucose intolerance. It has been demonstrated that knocking out the TNF-α and TNF-α receptor genes improves insulin resistance in several animal models of obesity-associated insulin resistance (Peraldi & Spiegleman, 1998; Hotamisigil, 1999). It is important to note that the improvement in insulin resistance with loss of TNF-α signalling is partial; therefore, other insulin-desensitising factors must exist. Resistin markedly decreases insulin-mediated glucose uptake (Steppan *et al*. 2001). More recently, it has been shown that IL-6 inhibits insulin transduction in hepatocytes (Senn *et al*. 2002). The insulin-desensitising effect of IL-6 has been confirmed *in vivo*. It is mediated by suppressor of cytokine signalling-3, which associates itself with the IR and insulin receptor substrate-1 and impedes insulin signalling (Senn *et al*. 2003).

Serum adipocytokine levels are elevated in obesity and interventions that reduce fat mass also lower adipocytokine levels. This relationship implies that approaches designed to reduce adipose tissue mass will attenuate the pro-inflammatory milieu that is associated with obesity-induced insulin resistance. Whilst most adipocytokines are

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associated with insulin resistance, greater levels of adiponectin are associated with improved insulin sensitivity by reversing insulin resistance associated with obesity and lipodystrophy (Yamauchi *et al*. 2001). Furthermore, plasma adiponectin levels are inversely associated with several risk factors for the metabolic syndrome, including adiposity (waist : hip ratio), insulin resistance, diastolic blood pressure, TAG concentrations and TNF-α receptor concentrations (Fernandez-Real *et al*. 2003). In addition, it appears that there is adipose tissue depot-specific adipocytokine expression. Visceral fat appears to produce several of these adipocytokines more actively than subcutaneous adipose tissue depots (Lyon *et al*. 2003). It has been estimated that abdominal fat may produce up to three times as much IL-6 as subcutaneous adipose tissue (Fruhbeck *et al*. 2001). Given the association between central obesity and the metabolic syndrome, it is interesting to speculate that visceral fat depots may express a greater proportion of the insulin-desensitising adipocytokines that directly affect peripheral insulin sensitivity.

Whilst there is strong evidence supporting the insulin-desensitising effects of adipocytokines, it should also be noted that this relationship may be more complex. Insulin itself induces an anti-inflammatory effect at the cellular level both *in vitro* and *in vivo*. A low-dose infusion of insulin reduces mononuclear cell reactive oxygen species generation, suppresses NF-κB DNA binding, induces inhibitor of κBα expression and suppresses concentrations of plasma intercellular adhesion cellular molecule-1, plasminogen-activator inhibitor-1 and monocyte chemotactic protein-1 (Dandona *et al*. 2001; Aljada *et al*. 2002).

The source of the pro-inflammatory profile in adipose tissue has been controversial. Relative to the classical inflammatory cells, adipocytes produce much smaller levels of cytokines. A very interesting recent study has demonstrated that obesity is associated with progressive infiltration of monocytes and macrophages into adipose tissue (Weisberg *et al*. 2004). It was shown using cell-specific gene expression analysis that adipose tissue macrophages are the source of almost all adipose tissue TNF-α expression and substantial amounts of inducible NO synthase and IL-6 expression. It was hypothesised that this process is initiated by adipocytes that secrete low levels of TNF-α, which in turn stimulates pre-adipocyte and endothelial cell macrophage chemo-attractant protein-1 and adipocytokine expression, and NEFA release, to further promote a pro-inflammatory and pro-oxidative state. The ultimate outcome is impaired adipocyte function and insulin resistance. With a greater understanding of the interaction between pro-inflammatory adipocytokines and metabolic stressors in obesity-induced insulin resistance, potential therapeutic strategies that attenuate pro-inflammatory insulin-desensitising adipocytokine expression in favour of the anti-inflammatory adipocytokines may be developed to promote metabolic health.

Fatty acids, inflammation and adipose tissue: nutrient regulation of gene expression

In terms of manipulating dietary factors to attenuate the inflammatory response in adipose tissue to improve insulin sensitivity, the most obvious treatment is to reduce adipose tissue mass. Indeed, several studies have shown that reduction of adipose tissue fat mass is associated with lower serum adipocytokine levels (Kahn & Flier, 2000). Nevertheless, the prevalence of obesity is increasing and because of poor compliance current therapies are largely ineffective. Thus, other strategies to attenuate the impact of insulin resistance in the presence of obesity are required. The author's group (Roche *et al*. 2002; Moloney *et al*. 2004) have demonstrated that a subgroup of fatty acids, known as conjugated linoleic acid (CLA), and in particular the *cis*-9, *trans*-11-CLA isomer, may have the potential to improve lipid metabolism and insulin sensitivity, within the context of obesity. This effect has been ascribed to differential sterol regulatory element-binding protein (SREBP)-1c gene expression, a key regulatory transcription factor involved in lipogenesis and glucose metabolism (Foretz *et al*. 1999; Shimomura *et al*. 2000; Gosmain *et al*. 2004). Feeding a *cis*-9, *trans*-11-CLA isomer-rich diet has divergent tissue-specific effects on SREBP-1c expression, markedly reducing hepatic SREBP-1c and increasing adipose tissue SREBP-1c expression, both of which could contribute to improved lipid and glucose metabolism (Roche *et al*. 2002). Interestingly this study has also shown TNF-α-regulated SREBP-1c expression in human adipocytes, but not in hepatocytes (Roche *et al*. 2002). This finding supports the hypothesis for cross-talk between molecular markers of insulin sensitivity and adipocytokines, which in turn can be modified by fatty acids. Subsequent work has shown that the *cis*-9, *trans*-11-CLA isomer-rich diet improves fasting glucose and insulin metabolism (Moloney *et al*. 2004). This improvement is associated with a marked reduction in adipose tissue TNF-α expression and lower NF-κB DNA binding, which has been attributed to lower nuclear P65 levels and increased cytosolic inhibitor of κBα expression (Moloney *et al*. 2004). Further work is required to determine the cell-specific nature of fatty acid interventions on molecular markers of insulin sensitivity and adipocytokine expression. Whilst CLA is a limited group of fatty acid isomers, this study has shown that fatty acids can modulate the interaction between the pro-inflammatory and metabolic stressors in adipose tissue and suggests that it may be possible to manipulate other fatty acids to attenuate the pro-inflammatory insulin-desensitising effect of obesity-induced insulin resistance.

Dietary fatty acid intervention studies and the metabolic syndrome

Several studies have shown a consistent relationship between plasma fatty acid composition and insulin resistance. A prospective cohort study (Laaksonen *et al*. 2002) has investigated the interaction between serum fatty acid composition and the development of impaired fasting glycaemia or T2DM in a cohort of middle-aged normoglycaemic men. It was found that at baseline the proportions of serum esterified and non-esterified saturated fatty acids (SFA) were increased and PUFA were decreased in men who after 4 years developed impaired fasting glycaemia or T2DM. This finding is also in line with recent epidemiological

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evidence from the Nurses' Health Study (Tanasescu *et al*. 2004), which shows that a higher intake of saturated fat and a low polyunsaturated fat : saturated fat are related to increased CVD risk among women with T2DM. This study also estimates that replacement of 5% energy from saturated fat with equivalent energy from carbohydrates or MUFA is associated with 22 and 37% lower risk of CVD respectively. This finding suggests that replacement of SFA by MUFA may be more effective at reducing CVD risk than low-fat high-carbohydrate diets.

Thus, several studies suggest a causal relationship between dietary fatty acid composition and insulin resistance. In comparison with the number of studies that have determined the relationship between dietary fatty acid composition and CVD risk factors, in particular lipoprotein metabolism, there are relatively few that have used insulin sensitivity as the primary metabolic end point. For the purpose of the present review, studies that have investigated the effect of isoenergetic substitution of dietary fatty acids and/or carbohydrates will be reviewed in order to exclude confounding effects associated with altered energy intake. The earlier dietary intervention studies that aimed to investigate this relationship have largely proved negative, which is probably related to methodological problems, including short study duration, inaccurate measures of insulin sensitivity and low statistical power.

More recently, the KANWU study, a controlled multicentre isoenergetic dietary intervention study involving 162 individuals (Vessby *et al*. 2001), has shown that decreasing dietary SFA and increasing MUFA improves insulin sensitivity but has no effect on insulin secretion. It is interesting to note that the favourable effect of substituting SFA for MUFA is only seen at a total fat intake of <37% energy. Within each dietary group a second assignment to fish oil supplementation or placebo was completed, but the addition of *n*-3 PUFA was found to have no effect on insulin sensitivity or insulin secretion, despite reduced TAG concentrations. The results of the KANWU study have been corroborated in a smaller randomised crossover dietary intervention study in fifty-nine young subjects (Perez-Jimenez *et al*. 2001). After a baseline saturated-fat diet subjects were randomly assigned to carbohydrate-rich and MUFA-rich diets for 28 d. The isoenergetic substitution of MUFA or carbohydrates for SFA was found to markedly improve insulin sensitivity to a similar extent *in vivo*. Furthermore, in *in vitro* studies both the carbohydrate-rich and MUFA-rich diets were shown to markedly increase basal and insulin-stimulated glucose uptake in monocytes. In contrast, a recent randomised double-blind crossover study comparing the effects of MUFA, SFA and *trans*-fatty acid diets (Lovejoy *et al*. 2002) failed to show any sizeable effect on insulin sensitivity or secretion. When the three dietary groups were sub-divided according to BMI, insulin sensitivity was found to be 24% lower in overweight individuals (BMI 25–30 kg/m^2) after the SFA diet compared with the MUFA diet. It is interesting to note that these diets were quite low in fat (28% energy); therefore, the effects of dietary fat composition may be more obvious without the background low-fat diet. Overall, human dietary intervention studies suggest that the removal of dietary saturated fat, as verified by alterations in plasma fatty acid composition, can have a direct effect on insulin sensitivity. This effect has also been confirmed in an acute study (Stefan *et al*. 2001) that has shown that altering the composition of infused NEFA affects insulin sensitivity. In six healthy subjects a SFA-rich lipid infusion was found to reduce the insulin sensitivity index (40–50%) to a much greater extent than a PUFA-rich lipid infusion (20–27%).

There are a number of positive health benefits associated with long-chain *n*-3 PUFA that are relevant to the metabolic syndrome, particularly in relation to TAG metabolism (Roche & Gibney, 2000). However, there is relatively little direct evidence that *n*-3 PUFA supplementation has positive effects on insulin sensitivity in man. Several animal studies have shown that feeding *n*-3 PUFA has positive effects on glucose and insulin metabolism in different models of T2DM and the metabolic syndrome (Storlien *et al*. 1987; Aguilera *et al*. 2004). Human epidemiological studies suggest that habitual dietary fish intake is inversely associated with the incidence of impaired glucose tolerance and T2DM (Feskens *et al*. 1985, 1991). Some studies have reported positive effects of *n*-3 PUFA supplementation on insulin sensitivity in individuals with impaired glucose tolerance and diabetes (Popp-Snijders *et al*. 1987; Fasching *et al*. 1991). Nevertheless, other studies have not shown a positive effect (Vessby *et al*. 2001). A recent study has investigated whether there is an interaction between background dietary *n*-6 PUFA and *n*-3 PUFA supplementation and insulin sensitivity in Indian Asians, a cohort particularly susceptible to the metabolic syndrome and T2DM (Brady *et al*. 2004). It was found that *n*-3 PUFA has no effect on insulin resistance (homeostasis model assessment of insulin resistance), even though *n*-3 PUFA supplementation is associated with improved fasting and postprandial TAG metabolism. Clearly, the putative effects of *n*-3 PUFA on human insulin resistance and impaired glucose tolerance require further clarification.

Diet–gene interactions: sensitive genotypes and dietary responsiveness

There is no doubt that the lack of consistency between studies can be partly ascribed to individualised metabolic variations, which could reflect a variable genetic background and/or environmental exposure. The search for the genetic basis of obesity and insulin resistance is fundamental to the understanding of the effects of dietary fatty acids and the metabolic syndrome. Several candidates have been proposed, all of which are associated with differing levels of promise. PPARγ plays a critical role in adipogenesis, insulin sensitivity and blood pressure (Barak *et al*. 1999; Barroso *et al*. 1999). Several studies have reported a relationship between a common PPARγ variant (Pro12Ala) and adiposity (Beamer *et al*. 1998). However, other studies have shown no association with BMI, insulin sensitivity and T2DM. A recent prospective population-based cohort study of the aetiology of T2DM (Luan *et al*. 2001) has shown an interesting interaction between habitual dietary fat composition and the PPARγ Pro12Ala polymorphism. An inverse relationship was found between both BMI and fasting insulin concentrations in the Ala carriers but not in

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the Pro homozygotes. This study highlights that gene–nutrient interactions, particularly with dietary fatty acids, are fundamental components of the pathology of common complex metabolic phenotypes.

Within the hypothesis that pro-inflammatory states are involved in the metabolic syndrome, common polymorphisms of cytokine genes have been associated with greater risk of the metabolic syndrome. The concomitant presence of polymorphisms of TNF-α (G308A) and IL-6 (C124G) in obese subjects with impaired glucose tolerance carries twice the risk of conversion to T2DM when compared with other genotypes. Also, a G308A mutation of the TNF-α promoter is associated with increased plasma TNF-α concentrations and a 1·8 higher risk of developing diabetes compared with non-carriers. It has also been shown that a C124G mutation of the IL-6 promoter increases the risk of insulin resistance (Kubaszek *et al*. 2003). As yet there has been no study of the interaction between the inflammatory polymorphism, diet and the metabolic syndrome. Nevertheless, it has been demonstrated that the extent to which fish oil supplementation can suppress peripheral blood mononuclear TNF-α production is modulated by polymorphisms in the TNF-α gene (Grimble *et al*. 2002). Finally, the concept of dietary responders and non-responders is an important issue. It is possible that individuals with a sensitive genotype who are susceptible to the metabolic syndrome may or may not respond to dietary fatty acid therapies. This concept is well characterised in the case of apoE polymorphisms, whereby some individuals will respond to dietary therapy, whereas other genotypes will not (Campos *et al*. 2001).

Conclusion

Dietary fatty acids play an integral role in the pathogenesis and prevention of the metabolic syndrome. Given the increasing prevalence of obesity a key objective should be to reduce the impact of modifiable risk factors, within the context of the obese phenotype. Whilst there is evidence to suggest that high-saturated-fat diets have deleterious effects on the metabolic syndrome, there is a paucity of information in relation to the most effective fatty acid intervention therapy. In addition, future research will have to take account of an individual's genetic background, both in terms of susceptibility to the metabolic syndrome and effective dietary responsiveness. With this information the true effectiveness of dietary therapies to reduce the health and economic burden associated with the metabolic syndrome will be understood.

References

Aguilera AA, Diaz GH, Barcelata ML, Guerrero OA & Ros RMO (2004) Effects of fish oil on hypertension, plasma lipids and tumor necrosis factor-α in rats with sucrose-induced metabolic syndrome. *Journal of Nutritional Biochemistry* **15**, 350–357.

Alberti K & Zimmet P (1998) Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: Diagnosis and classification of diabetes mellitus, provisional report of a WHO consultation. *Diabetic Medicine* **15**, 539–553.

Aljada A, Ghanim H, Mohanty P, Kapur N & Dandona P (2002) Insulin inhibits the pro-inflammatory transcription factor early growth response gene-1 (Egr)-1 expression in mononuclear cells (MNC) and reduces plasma tissue factor (TF) and plasminogen activator inhibitor-1 (PAI-1) concentrations. *Journal of Clinical Endocrinology and Metabolism* **87**, 1419–1422.

Barak Y, Nelson MC, Ong ES, Jones YZ, Ruiz-Lozano P, Chien KR, Koder A & Evans RM (1999) PPAR gamma is required for placental, cardiac, and adipose tissue development. *Molecular Cell* **4**, 585–595.

Barroso I, Gurnell M, Crowley VE, Agostini M, Schwabe JW, Soos MA, Maslen GL, Williams TD, Lewis H, Schafer AJ, Chatterjee VK & O'Rahilly S (1999) Dominant negative mutations in human PPARgamma associated with severe insulin resistance, diabetes mellitus and hypertension. *Nature* **402**, 880–883.

Beamer BA, Yen CJ, Andersen RE, Muller D, Elahi D, Cheskin LJ, Andres R, Roth J & Shuldiner AR (1998) Association of the Pro12Ala variant in the peroxisome proliferator-activated receptor-gamma2 gene with obesity in two Caucasian populations. *Diabetes* **47**, 1806–1808.

Brady LM, Lovegrove SS, Lesauvage SV, Gower BA, Minihane AM, Williams CM & Lovegrove JA (2004) Increased n-6 polyunsaturated fatty acids do not attenuate the effects of long-chain n-3 polyunsaturated fatty acids on insulin sensitivity or triacylglycerol reduction in Indian Asians. *American Journal of Clinical Nutrition* **79**, 983–991.

Campos H, D'Agostino M & Ordovas JM (2001) Gene-diet interactions and plasma lipoproteins: role of apolipoprotein E and habitual saturated fat intake. *Genetic Epidemiology* **20**, 117–128.

Dandona P, Aljada A & Bandyopadhyay A (2004) Inflammation: the link between insulin resistance, obesity and diabetes. *TRENDS in Immunology* **25**, 4–7.

Dandona P, Aljada A, Mohanty P, Ghanim H, Hamouda W, Assian E & Ahmad S (2001) Insulin inhibits intranuclear nuclear factor kappaB and stimulates IkappaB in mononuclear cells in obese subjects: evidence for an anti-inflammatory effect? *Journal of Clinical Endocrinology and Metabolism* **86**, 3257–3265.

Fasching P, Ratheiser K, Waldhausl W, Rohac M, Osterrode W, Nowotny P & Vierhapper H (1991) Metabolic effects of fish-oil supplementation in patients with impaired glucose tolerance. *Diabetes* **40**, 583–589.

Fernandez-Real JM, Lopez-Bermejo A, Casamitjana R & Ricart W (2003) Novel interactions of adiponectin with the endocrine system and inflammatory parameters. *Journal of Clinical Endocrinology and Metabolism* **88**, 2714–2718.

Feskens EJ, Bowles CH & Kromhout D (1991) Inverse association between fish intake and risk of glucose intolerance in normoglycemic elderly men and women. *Diabetes Care* **14**, 935–941.

Feskens EJ, Virtanen SM, Rasanen L, Tuomilehto J, Stengard J, Pekkanen J, Nissinen A & Kromhout D (1985) Dietary factors determining diabetes and impaired glucose tolerance. A 20-year follow-up of the Finnish and Dutch cohorts of the Seven Countries Study. *Diabetes Care* **18**, 1104–1112.

Foretz M, Guichard P, Frerre C & Foufelle F (1999) Sterol regulatory element-binding protein-1c is a major mediator of insulin action gene expression, a key regulatory transcription factor on the hepatic expression of glucokinase and lipogenesis-related genes. *Proceedings of the National Academy of Sciences USA* **96**, 12737–12742.

Fruhbeck G, Gomez-Ambrosi J, Muruzabal FJ & Burrell MA (2001) The adipocyte: a model for integration of endocrine and metabolic signaling in energy metabolism regulation. *American Journal of Physiology* **280**, E827–E847.

Gosmain Y, Lefai E, Rysner S, Roques M & Vidal H (2004) Sterol regulatory element-binding protein-1 mediates the effect of insulin on hexokinase II gene expression in human muscle cells. *Diabetes* **53**, 321–329.

Grimble RF, Howell WM, O'Reilly G, Turner SJ, Markovic O, Hirrell S, East JM & Calder PC (2002) The ability of fish oil to suppress tumor necrosis factor alpha production by peripheral blood mononuclear cells in healthy men is associated with polymorphisms in genes that influence tumor necrosis factor alpha production. *American Journal of Clinical Nutrition* **76**, 454–459.

Hotamisigil GS (2003) Inflammatory pathways and insulin action. *International Journal of Obesity* **27**, S53–S55.

Hotamisigil GS (1999) The role of TNF-alpha and TNF receptors in obesity and insulin resistance. *Journal of Internal Medicine* **245**, 621–625.

Isomaa B, Almgren P, Tuomi T, Forsen B, Lahti K, Nissen M, Taskinen MR & Groop L (2001) Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care* **24**, 683–689.

Kahn BB & Flier JS (2000) Obesity and insulin resistance. *Journal of Clinical Investigation* **106**, 473–481.

Kim JK, Kim YJ, Fillmore JJ, Chen Y, Moore I, Lee J, Yuan M, Li ZW, Karin M, Perret P, Shoelson SE & Shulman GI (2001) Prevention of fat-induced insulin resistance by salicylate. *Journal of Clinical Investigation* **108**, 437–446.

King H, Aubert RE & Herman WH (1998) Global burden of diabetes 1995–2025. *Diabetes Care* **21**, 1414–1431.

Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA & Nathan DM (2002) Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *New England Journal of Medicine* **7**, 393–403.

Kubaszek A, Pihlajamaki J, Komarovski V, Lindi V, Lindstrom J, Eriksson J *et al.* (2003) Finnish Diabetes Prevention Study. Promoter polymorphisms of the TNF-alpha (G-308A) and IL-6 (C-174G) genes predict the conversion from impaired glucose tolerance to type 2 diabetes: the Finnish Diabetes Prevention Study. *Diabetes* **52**, 1872–1876.

Laaksonen DE, Lakkat TA, Lakkat H-M, Nyyssonent K, Rissanent T, Niskanen LK & Salonen JY (2002) Serum fatty acid composition predicts development of impaired fasting glycaemia and diabetes in middle-aged men. *Diabetes Medicine* **19**, 456–464.

Le Marchand-Brustel Y, Gaul P, Gremeaux T, Gonzalez T, Barres R & Tanti J-F (2003) Fatty acid-induced insulin resistance: role of insulin receptor substrate 1 serine phosphorylation in the retroregulation of insulin signalling. *Biochemical Society Transactions* **31**, 1152–1156.

Lovejoy JC, Smith SR, Champagne CM, Most MM, Lefevre M, DeLany JP, Denkins YM, Rood JC, Veldhuis J & Bray GA (2002) Effects of diets enriched in saturated (palmitic), monounsaturated (oleic), or trans (eladic) fatty acids in insulin sensitivity and substrate oxidation in healthy adults. *Diabetes Care* **25**, 1283–1288.

Luan J, Browne PO, Harding AH, Halsall DJ, O'Rahilly S, Chatterjee VK & Wareham NJ (2001) Evidence for gene-nutrient interaction at the PPARgamma locus. *Diabetes* **50**, 686–689.

Lyon CJ, Law RE & Hsueh WA (2003) Adiposity, inflammation and atherogenesis. *Endocrinology* **144**, 2195–2200.

Mann JI (2002) Diet and risk of coronary heart disease and type 2 diabetes. *Lancet* **360**, 783–789.

Moloney F, Noone E, Loscher C, Gibney MJ & Roche HM (2004) *Cis*-9, *trans*-11 conjugated linoleic acid improves metabolic and molecular markers of insulin sensitivity in adipose tissue and liver. *Proceedings of the Nutrition Society* **63**, 58A.

National Cholesterol Education Program Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) (2001) Executive Summary of The Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *Journal of the American Medical Association* **285**, 2486–2497.

Peraldi P & Spiegleman B (1998) TNF-alpha and insulin resistance: summary and future prospects. *Molecular Cell Biochemistry* **182**, 169–175.

Perez-Jimenez E, Lopez-Miranda J, Pinillos MD, Gomez P, Paz-Rojas E, Montilla P, Marin C, Velasco MJ, Blanco-Molina A, Jimenez Pereperez JA & Ordovas JM (2001) A Mediterranean and a high-carbohydrate diet improve glucose metabolism in healthy young persons. *Diabetologia* **44**, 2038–2043.

Popp-Snijders C, Schouten JA, Heine RJ, van der Meer J & van der Veen EA (1987) Dietary supplementation of omega-3 polyunsaturated fatty acids improves insulin sensitivity in non-insulin-dependent diabetes. *Diabetes Research* **4**, 141–147.

Roche HM & Gibney MJ (2000) The effect of long-chain n-3 PUFA on fasting and postprandial triacylglycerol metabolism. *American Journal of Clinical Nutrition* **71**, 232–237.

Roche HM, Noone E, Sewter C, McBennett S, Savage D, Gibney MJ, O'Rahilly S & Vidal-Puig AJ (2002) Isomer dependent metabolic effects of conjugated linoleic acid (CLA), insights from molecular markers: SREBP-1c and LXRα. *Diabetes* **51**, 2037–2044.

Saltiel AR (2000) The molecular and physiological basis of insulin resistance: emerging implications for metabolic and cardiovascular diseases. *Journal of Clinical Investigation* **106**, 163–164.

Senn JJ, Klover PJ, Nowak IA & Mooney RA (2002) Interleukin-6 induces cellular insulin resistance in hepatocytes. *Diabetes* **51**, 3391–3399.

Senn JJ, Klover PJ, Nowak IA, Zimmers TA, Koniaris LG, Furlanetto RW & Mooney RA (2003) Suppressor of cytokine signaling-3 (SOCS-3), a potential mediator of interleukin-6-dependent insulin resistance in hepatocytes. *Journal of Biological Chemistry* **278**, 13740–13746.

Shimomura I, Matsuda M, Hammer RE, Bashmakov Y, Brown MS & Goldstein JL (2000) Decreased IRS-2 and increased SREBP-1c lead to mixed insulin resistance and sensitivity in livers of lipodystrophic and ob/ob mice. *Molecular Cell* **6**, 77–86.

Stefan N, Wahl HG, Fritsche A, Haring H & Stumvoll M (2001) Effect of the pattern of elevated free fatty acids on insulin sensitivity and insulin secretion in healthy humans. *Hormone Metabolism Research* **33**, 432–438.

Steppan CM, Bailey ST, Bhat S, Brown EJ, Banerjee RR, Wright CM, Patel HR, Ahima RS & Lazar MA (2001) The hormone resistin links obesity to diabetes. *Nature* **409**, 307–312.

Storlien LH, Kraegen EW, Chisholm DJ, Ford GL, Bruce DG & Pascoe WS (1987) Fish oil prevents insulin resistance induced by high fat feeding in rats. *Science* **237**, 885–888.

Tanasescu M, Cho E, Manson JE & Hu FB (2004) Dietary fat and cholesterol and the risk of cardiovascular disease among women with type 2 diabetes. *American Journal of Clinical Nutrition* **79**, 99–105.

Vessby B, Uusitupa M, Hermansen K, Riccardi G, Rivellese AA, Tapsell LC *et al.* (2001) Substituting dietary saturated for monounsaturated fat impairs insulin sensitivity in healthy men and women: The KANWU study. *Diabetologia* **44**, 312–319.

Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL & Ferrante AW Jr (2004) Obesity is associated with macrophage

accumulation in adipose tissue. *Journal of Clinical Investigation* **112**, 1796–1808.
Yamauchi T, Kamon J, Waki H, Terauchi Y, Kubota N, Hara K *et al.* (2001) The fat-derived hormone adiponectin reverses insulin resistance associated with both lipoatrophy and obesity. *Nature Medicine* **7**, 941–946.
Zick Y (2001) Insulin resistance: a phosphorylation-based uncoupling of insulin signalling. *TRENDS in Cell Biology* **11**, 437–441.
Zimmet P, Alberti KGMM & Shaw J (2001) Global and societal implications of the diabetes epidemic. *Nature* **414**, 782–787.

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