Clinical Endocrinology (2012) 77, 508–512 doi: 10.1111/j.1365-2265.2012.04450.x

CLINICAL QUESTION

What dietary modification best improves insulin sensitivity and why?

Martin O. Weickert*,†

*Warwickshire Institute for the Study of Diabetes, Endocrinology and Metabolism, University Hospitals Coventry and Warwickshire NHS Trust, and †Clinical Sciences Research Institute, Warwick Medical School, University of Warwick, Coventry, UK

Summary

Insulin resistance (IR) has been proposed as the strongest single predictor for incident type 2 diabetes and is mainly caused by adiposity as a result of chronic excessive energy intake. Loss of body weight and fat mass improve insulin sensitivity. However, independent of energy intake and changes in body weight/composition, dietary content and specific metabolic effects of certain nutrients may play significant additional roles in influencing IR. These effects are mainly relatively modest, with modulation of IR and diabetes risk within the range of 10–30%, but could be of major relevance on a population level. Examples include dietary concepts and patterns such as the traditional Mediterranean diet; the isoenergetic modulation of the composition of types of fatty acids in the diet; low-carbohydrate–high-protein diets; the quality of carbohydrate-rich foods, which includes the concepts of glycaemic index (GI) and glycaemic load; and, not necessarily related to the GI concept, specific metabolic effects of high-fibre diets, with relevant differences between the type of fibre consumed. Effects of further selected foods (e.g. coffee, tea and nuts) and micronutrients (e.g. magnesium, selenium and zinc) on the modulation of IR have been reviewed elsewhere. This study focuses on changes in IR by isoenergetic modulation of the main macronutrients (fat, carbohydrates including dietary fibre, and dietary protein), with discussion of novel concepts and the potential interplay of food components in the current dietary concepts.

(Received 4 April 2012; returned for revision 09 May 2012; finally revised 11 May 2012; accepted 23 May 2012)

Introduction

Insulin resistance (IR) is mainly caused by excessive energy intake leading to adiposity and has been proposed as the strongest single predictor for type 2 diabetes (T2DM).[1] As weight loss almost always improves insulin sensitivity,[2] any balanced, energy-reduced and safe diet that can be sustained in the long term could be used to reduce IR. Isoenergetic changes in the macronutrient composition and the quality of ingested foods such as Mediterranean style diets may exert additional important effects on IR, independent of weight loss.[3–6] Physical activity and particularly the participation in regular structured exercise programmes are further factors that decrease IR both acutely and in the long term,[7] but discussing this topic is beyond the scope of this paper.

Correspondence: Martin O. Weickert, Warwickshire Institute for the Study of Diabetes, Endocrinology and Metabolism, University Hospitals Coventry and Warwickshire NHS Trust, Coventry, UK. Tel.: 0044 2476 965968; Fax: 0044 2476 965964; E-mail: m.weickert@warwick.ac.uk

Isoenergetic modulation of dietary fat content

Dietary fat is a mixture of fatty acids (FA), with saturated (SFA), *trans*-unsaturated (TFA), monounsaturated (MUFA) and polyunsaturated FA (PUFA; further classified as n-3 and n-6 PUFA) as the main components.[5] Excessive intake of total fat (>37% of daily energy intake[8]), irrespective of FA composition, may worsen IR, likely *via* a combination of factors that include interference with binding of insulin to its receptors and accumulation of triglycerides in skeletal muscle.[5] However, if total fat intake remains <30%, the type of FA consumed appears to differently influence IR.[8]

Substitution of SFA by MUFA reduces IR by approximately10%.[8] SFA are generally assumed to drive IR, possibly related to SFA-mediated increases in intramyocellular lipid content which is causally related to IR.[5] Further SFA-induced actions may include interference with cell membrane function, inflammatory pathways, endoplasmatic reticulum stress and toxic effects on pancreatic beta-cells.[5] Otherwise, evidence is emerging that SFA are a complex family of substances differing in function, structure and metabolic effects, with some SFA playing important and specific biological roles.[5] A high dairy intake, a source that contains approximately 70% of SFA, has been associated with reduced diabetes risk.[4] However, stronger associations with low-fat and fat-free dairy products suggest that dairy fat *per se* is unlikely to be the driving factor.[4] These examples highlight the difficulties when trying to map single components of complex foods to a metabolic outcome.

The underlying mechanisms involved in MUFA-induced improvement of IR are incompletely understood but may

© 2012 Blackwell Publishing Ltd

involve effects on cell membrane FA composition,[4] with functional effects on membrane fluidity, ion permeability, insulin receptor binding/affinity[4] and up-regulation of glucose transporters.[5] Alterations in incretin responses and beta-cell function might be further involved.[5] Despite these findings, MUFA are not associated with reduced risk of T2DM in prospective cohort studies.[9]

Polyunsaturated fatty acids appear to modulate IR depending on the type of PUFA consumed (n-3 or n-6) and with diverse effects in humans and animal models. In rodents, supplementation with n-3 PUFA from marine origin, but not with n-6 PUFA, prevents and reverses IR, probably related to anti-inflammatory actions and the regulation of the expression of genes involved in carbohydrate and lipid metabolism. In contrast, in humans, n-6 PUFA may improve IR and probably also diabetes risk,[4] whereas results for n-3 PUFA are inconsistent and generally fail to show relevant effects on these outcomes.[2,4] Some PUFA suppress lipogenic gene expression *in vitro*,[4] partly by PPAR gamma–mediated effects, which may be related to beneficial effects of n-6 PUFA consumption in humans.

The adverse effects of TFA on cardiovascular disease are well established, but their role in the development of IR and T2DM is less clear.[4] Studies in rats have shown that TFA induce IR, even when compared with SFA-rich diets.[5] The Nurses' Health Study showed a dose-dependent association between TFA intake and risk of T2DM, probably related to a TFA-induced increase in inflammatory cytokines.[4] However, the concept that inflammation is causally involved in the development of diabetes has not been proven; our own studies showed that pretreatment with acetylsalicylic acid attenuated lipid-induced IR in healthy humans unrelated to changes of circulating inflammatory markers.[10] To date, no long-term randomized trials exist that have investigated the effect of dietary fat composition on diabetes risk. The effects of various dietary modifications including the modulation of fat content in the diet are summarized in Table 1.

Quality of carbohydrates

The modest success of low-fat diets has prompted research on alternative strategies, including low-glycaemic-index (GI) diets. Conventional high-carbohydrate diets increase postprandial glucose and insulin concentrations and may compromise fat oxidation, fuel partitioning and metabolic flexibility.[11,12] Increasing the GI of foods has been independently linked to higher prevalence of IR in observational studies, whereas low-GI diets improved whole-body IR in patients with T2DM.[11] However, not all studies show protective effects of low-GI diets on IR and diabetes risk,[6,13] and many low-GI diets are also rich in cereal fibre that complicates interpretation of results and separation of effects.[6] In fact, a recent study that claimed superiority of low-GI *vs* high-cereal-fibre diets provided higher cereal-fibre contents in the low-GI group,[14] again highlighting the difficulties when trying to assess the metabolic effects of single components of complex foods.

Dietary fibre

Many assume that the strong associations between fibre intake and reduced diabetes risk[15,16] are mainly related to viscous and/or gel-forming properties of soluble fibre from fruit and vegetables that influence the GI and blood lipids, and potentially beneficial metabolic effects of short-chain fatty acids (SCFA) derived from colonic fermentation of nondigested fibre by the gut microbiota.[6,17] However, in the few available long-term studies (>45 weeks) in rodents, in otherwise identical diets only differing in soluble/fermentable (guar) *vs* insoluble/nonfermentable fibre (cereal-fibre extract) content the short-term beneficial effects of soluble fibre were abolished,[6,18] likely explained by a cumulative contribution of SCFA to total energy intake which resulted in a more obese, IR phenotype.[18] This effect could be relevant also in humans.[6,19] Notably, meta-analyses of large prospective cohort studies show markedly reduced diabetes risk with high cereal-fibre intake [relative risk for extreme quintiles (RR), 0·67; 95% CI, 0·62–0·72], but not any associations with fruit (RR, 0·96; 95% CI, 0·88–1·04) or vegetable (RR, 1·04; 95% CI, 0·94–1·15) intake.[16] Importantly, the main sources of cereal fibre in US prospective cohort studies are cellulose and hemicelluloses from wheat bran[6] that are insoluble in water, nonviscous and only moderately fermentable.[6,20]

Recently, it has been shown that cereal-fibre intake, under isoenergetic conditions, improves whole-body IR in both short-term and more prolonged studies, as measured using euglycaemic–hyperinsulinaemic clamps.[6,21,22] These effects appear to be dose dependent[6] but independent of colonic fermentation, changes in dominant groups of the gut microbiota or circulating glucagon-like peptide-1 (GLP-1).[6,20,22] We have recently proposed a novel concept that could contribute to explaining improved IR with cereal-fibre intake, showing that cereal fibre may hinder the digestion and/or absorption of dietary protein in the upper gut, thereby preventing amino acid–induced IR.[22,23] However, this concept needs to be confirmed in independent studies, and further, yet unknown mechanisms may be additionally involved; examples include cereal-fibre-induced modulation of bile acid binding and metabolite profiles.

High-protein (HP) diets

High-protein diets beneficially influence blood lipids, body composition and weight loss, at least in the short term.[24] Better weight loss with HP diets may be explained by the satiating effects of dietary protein, reduced choice of foods and an aversion to dietary fat in the absence of carbohydrates. Lowering the per cent protein of the diet from 15% to 10% results in higher total energy intake, predominantly from savoury-flavoured foods available between meals,[25] further indicating that a higher dietary protein intake may help to reduce energy intake. However, sustained weight loss with any diet is difficult to achieve, and the reported rapid onset of IR in healthy humans exposed to amino acid infusions is a concern,[23] with inhibition of glucose uptake being driven through phosphorylation of downstream

© 2012 Blackwell Publishing Ltd

Table 1. Effects of dietary modifications on insulin resistance (IR) and diabetes risk

Dietary intervention	Weight loss (short term, up to 2 years)	Insulin resistance	Diabetes risk	Other effects
Energy-reduced diet (sustained)	Strong benefit	Strong benefit[1,2]	Strong benefit[9]	
Reduction in total fat (<30%)	Modest benefit; less effective than low-carbohydrate, high-protein (HP) diets[5,24]	Modest benefit; but increased IR with excessive fat intake (>37%)[2,4,5,8]	Probably reduced[9]	Lowers LDL cholesterol; reduces risk for CVD[2,4,5]
Reduction of SFA (<7%)	Unknown if total energy intake is not reduced	Probably beneficial[2,4,5,8]	Unknown[2,4,5,8]	Lowers LDL cholesterol; reduces risk for CVD[2,4,5]
Reduction of TFA (as low as possible)	Unknown if total energy intake is not reduced	Inconsistent; probably modest benefit (animal studies)[2,4,5,8]	Probably reduced, dose dependent (Nurses Health)[4,5,8]	Reduced risk for CVD; lowers LDL and increases HDL cholesterol, inflammatory cytokines[4]
Increase in MUFA (>10%)	Unknown if total energy intake is not reduced	Modest benefit[5,8]	No benefit shown[9]	Lowers LDL cholesterol, triacylglycerols, blood pressure[2,4,5,9]
Increase in PUFA (>10%)	Unknown if total energy intake is not reduced	Dependent on type and species[4,9]	Unknown[4,5,9]	Probably beneficial effects on inflammatory cytokines, adipokines; lowers LDL cholesterol[5]
n-3 PUFA		No benefit in humans[4,9]	No benefit shown, probably adverse[9]	Probably reduction in LDL cholesterol and triacylglycerols[5]
n-6 PUFA		Modest benefit[4,5,9]	Unknown[4,5,9]	
Low-carbohydrate diets	Modest benefit, at least in the short term[24]	Unknown, perhaps adverse in HP setting[22,23,26,30]	Unknown[4,5,9]	Beneficial effects on HDL cholesterol and triacylglycerols. LDL cholesterol higher-*vs* low-fat diets.[5,24] Minimum of 130 g/day is recommended to provide adequate supply to CNS
HP intake	Benefit, at least in the short term[24,27]	Adverse, at least under isoenergetic conditions[22,23,26,30]	Probably adverse; probably most pronounced with red meat intake[29]	Beneficial on HDL, LDL cholesterol, blood pressure, increased satiety[5,24]
Low-GI diets	Modest benefit[11]	Perhaps modest benefit, controversial[6,11,13]	Perhaps modest benefit, controversial[6,11,13]	Improved LDL cholesterol, inflammatory markers, probably reduced cardiovascular risk[11]
Dietary fibre (>14 g/1000 kcal and day)	Modest benefit[6]	Controversial[6]	Beneficial[6]	
Soluble fibre (main sources: fruit and vegetables)	Modest benefit[6]	No consistent effect in human studies[6]	No effect[15,16]	Lowers GI, LDL cholesterol, triacylglycerols[6]
Insoluble cereal fibre (main sources: cereals, wheat bran and whole grain products)	Modest benefit[6]	Improved, likely dose dependent, independent of weight loss[6,21,22]	Strong benefit[15,16]	
Simple sugars	Inconsistent in humans, probably adverse[2]	Inconsistent in humans; probably adverse[2]	Unknown[2]	
Mediterranean style diets	Modest benefit[2,3]	Beneficial[2,3]	Beneficial[2,3]	Reduced risk for CVD, lower inflammatory cytokines, improved lipid profiles; increased survival[2,3]

LDL, low-density lipoprotein; HDL, high-density lipoprotein; CVD, cardiovascular disease; CNS, central nervous system; SFA, saturated fatty acids; TFA, *trans*-unsaturated fatty acids; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids; GI, glycaemic index.

factors of the insulin signalling cascade by the translation initiation factor serine-kinase-6-1 (S6K1).[23] In agreement with this, long-term HP intake results in whole-body IR,[22,26] associated with the up-regulation of factors involved in the mammalian-target-of-rapamycin (mTOR)/S6K1 signalling pathway,[22] increased stimulation of glucagon and insulin within the endocrine pancreas, high glycogen turnover[26] and stimulation of gluconeogenesis.[22,26]

In the short term, these negative effects on IR may be compensated by HP diet–induced weight loss and, at least in

© 2012 Blackwell Publishing Ltd

physically active people, increases in lean (muscle) mass that are also mediated *via* the mTOR/S6K1 pathway. However, most subjects that expose themselves to weight loss diets are overweight/obese and typically sedentary. Furthermore, relevant long-term sustained weight loss with HP diets has not been proven to date. In the Diet, Obesity and Genes (DiOGenes) trial, maintenance of weight loss was only marginally better with a HP intake and failed to reach significance in the full model, despite the large number of 548 completers in this European multicentre study.[27] In DiOGenes, we have also shown that HP intake (and high-GI carbohydrates) may increase low-grade inflammation.[28] possibly further related to worsening of whole-body IR.

In further agreement that HP diets may deteriorate glucose metabolism, it was recently shown in a large prospective cohort with 10-year follow-up that consuming 5% of energy from both animal and total protein at the expense of carbohydrates or fat increases diabetes risk by 30%.[29] The Carnivore Connection Hypothesis[30] suggests that during human evolution, a scarcity of dietary carbohydrates together with high intake from animal proteins led to IR. This may have provided a survival and reproductive advantage by redirecting glucose from maternal use to foetal metabolism, as such increasing birthweight and survival of the offspring,[30] but could have deleterious effects in a high carbohydrate environment. In this context, it is interesting that populations who have only recently switched dietary habits from traditional HP hunter–gatherer to modern high carbohydrate intake show excessively high prevalence of IR and T2DM, as compared to European populations that switched to higher carbohydrate intake some 12 000 years ago.[30]

There is an ongoing steep increase in the prevalence of obesity, IR and T2DM, despite the currently widespread use of various HP dietary strategies. May this suggest that these diets are unsuitable in overweight, physically inactive patients at risk of developing T2DM?

Conclusions

Reduced energy intake combined with physical exercise remains the mainstay tool for improving insulin sensitivity by lifestyle measures. With the currently available evidence, additional dietary measures that may reduce IR include the following: (i) using a Mediterranean-like dietary pattern, but avoiding excess intake of dietary fat; (ii) substituting SFA and TFA by MUFA and n-6 PUFA; (iii) and emphasizing the cereal fibre content in the diet and keeping exercise levels high, particularly when choosing a HP diet. Mediterranean style diets may be not too complex to adhere to and tick many of these boxes.

Acknowledgements

I have no conflicts of interest. I apologize to all the researchers whose work was not cited because of the constraints on the number of references.

Conflict of interest

The author assures that there were no conflicts of interest.

References

1 Sung, K.C., Jeong, W.S., Wild, S.H. *et al.* (2012) Combined influence of insulin resistance, overweight/obesity, and fatty liver as risk factors for type 2 diabetes. *Diabetes Care*, **35**, 717–722.
2 McAuley, K. & Mann, J. (2006) Thematic review series: patient-oriented research. Nutritional determinants of insulin resistance. *Journal of Lipid Research*, **47**, 1668–1676.
3 Kastorini, C.M., Milionis, H.J., Esposito, K. *et al.* (2011) The effect of Mediterranean diet on metabolic syndrome and its components: a meta-analysis of 50 studies and 534,906 individuals. *Journal of the American College of Cardiology*, **57**, 1299–1313.
4 Riserus, U., Willett, W.C. & Hu, F.B. (2009) Dietary fats and prevention of type 2 diabetes. *Progress in Lipid Research*, **48**, 44–51.
5 Thomas, T. & Pfeiffer, A.F. (2011) Foods for the prevention of diabetes: how do they work? *Diabetes Metabolism Research and Reviews*, **28**, 25–49.
6 Weickert, M.O. & Pfeiffer, A.F. (2008) Metabolic effects of dietary fiber consumption and prevention of diabetes. *Journal of Nutrition*, **138**, 439–442.
7 Zisser, H., Gong, P., Kelley, C.M. *et al.* (2011) Exercise and diabetes. *International Journal of Clinical Practice. Supplement*, **7**, 1–75.
8 Vessby, B., Uusitupa, M., Hermansen, K. *et al.* (2001) Substituting dietary saturated for monounsaturated fat impairs insulin sensitivity in healthy men and women: the KANWU Study. *Diabetologia*, **44**, 312–319.
9 Salas-Salvado, J., Martinez-Gonzalez, M.A., Bullo, M. *et al.* (2011) The role of diet in the prevention of type 2 diabetes. *Nutrition, Metabolism, and Cardiovascular Diseases*, **21**(Suppl. 2), B32–B48.
10 Möhlig, M., Freudenberg, M., Bobbert, T. *et al.* (2006) Acetylsalicylic acid improves lipid-induced insulin resistance in healthy men. *Journal of Clinical Endocrinology and Metabolism*, **91**, 964–967.
11 Brand-Miller, J. & Buyken, A.E. (2012) The glycemic index issue. *Current Opinion in Lipidology*, **23**, 62–67.
12 Isken, F., Klaus, S., Petzke, K.J. *et al.* (2010) Impairment of fat oxidation under high- vs. low-glycemic index diet occurs before the development of an obese phenotype. *American Journal of Physiology and Endocrinology Metabolism*, **298**, E287–E295.
13 Pi-Sunyer, X. (2005) Do glycemic index, glycemic load, and fiber play a role in insulin sensitivity, disposition index, and type 2 diabetes? *Diabetes Care*, **28**, 2978–2979.
14 Jenkins, D.J., Kendall, C.W., McKeown-Eyssen, G. *et al.* (2008) Effect of a low-glycemic index or a high-cereal fiber diet on type 2 diabetes: a randomized trial. *JAMA*, **300**, 2742–2753.
15 de Munter, J.S., Hu, F.B., Spiegelman, D. *et al.* (2007) Whole grain, bran, and germ intake and risk of type 2 diabetes: a prospective cohort study and systematic review. *PLoS Medicine*, **4**, e261.
16 Schulze, M.B., Schulz, M., Heidemann, C. *et al.* (2007) Fiber and magnesium intake and incidence of type 2 diabetes: a prospective study and meta-analysis. *Archives of Internal Medicine*, **167**, 956–965.

© 2012 Blackwell Publishing Ltd

17 Delzenne, N.M. & Cani, P.D. (2011) Gut microbiota and the pathogenesis of insulin resistance. *Current Diabetes Reports*, **11**, 154–159.
18 Isken, F., Klaus, S., Osterhoff, M. *et al.* (2010) Effects of long-term soluble vs. insoluble dietary fiber intake on high-fat diet-induced obesity in C57BL/6J mice. *Journal of Nutritional Biochemistry*, **21**, 278–284.
19 McNeil, N.I. (1984) The contribution of the large intestine to energy supplies in man. *American Journal of Clinical Nutrition*, **39**, 338–342.
20 Weickert, M.O., Arafat, A.M., Blaut, M. *et al.* (2011) Changes in dominant groups of the gut microbiota do not explain cereal-fiber induced improvement of whole-body insulin sensitivity. *Nutrition and Metabolism*, **8**, 90.
21 Pereira, M.A., Jacobs, D.R. Jr, Pins, J.J. *et al.* (2002) Effect of whole grains on insulin sensitivity in overweight hyperinsulinemic adults. *American Journal of Clinical Nutrition*, **75**, 848–855.
22 Weickert, M.O., Roden, M., Isken, F. *et al.* (2011) Effects of supplemented isoenergetic diets differing in cereal fiber and protein content on insulin sensitivity in overweight humans. *American Journal of Clinical Nutrition*, **94**, 459–471.
23 Tremblay, F., Krebs, M., Dombrowski, L. *et al.* (2005) Overactivation of S6 kinase 1 as a cause of human insulin resistance during increased amino acid availability. *Diabetes*, **54**, 2674–2684.
24 Hession, M., Rolland, C., Kulkarni, U. *et al.* (2009) Systematic review of randomized controlled trials of low-carbohydrate vs. low-fat/low-calorie diets in the management of obesity and its comorbidities. *Obesity Reviews*, **10**, 36–50.
25 Gosby, A.K., Conigrave, A.D., Lau, N.S. *et al.* (2011) Testing protein leverage in lean humans: a randomised controlled experimental study. *PLoS One*, **6**, e25929.
26 Linn, T., Santosa, B., Gronemeyer, D. *et al.* (2000) Effect of long-term dietary protein intake on glucose metabolism in humans. *Diabetologia*, **43**, 1257–1265.
27 Larsen, T.M., Dalskov, S.M., van Baak, M. *et al.* (2010) Diets with high or low protein content and glycemic index for weight-loss maintenance. *New England Journal of Medicine*, **363**, 2102–2113.
28 Gögebakan, O., Kohl, A., Osterhoff, M.A. *et al.* (2011) Effects of weight loss and long-term weight maintenance with diets varying in protein and glycemic index on cardiovascular risk factors: the diet, obesity, and genes (DiOGenes) study: a randomized, controlled trial. *Circulation*, **124**, 2829–2838.
29 Sluijs, I., Beulens, J.W., van der, A.D. *et al.* (2010) Dietary intake of total, animal, and vegetable protein and risk of type 2 diabetes in the European Prospective Investigation into Cancer and Nutrition (EPIC)-NL study. *Diabetes Care*, **33**, 43–48.
30 Brand-Miller, J.C., Griffin, H.J. & Colagiuri, S. (2012) The carnivore connection hypothesis: revisited. *Journal of Obesity*, **2012**, 258624.

© 2012 Blackwell Publishing Ltd