

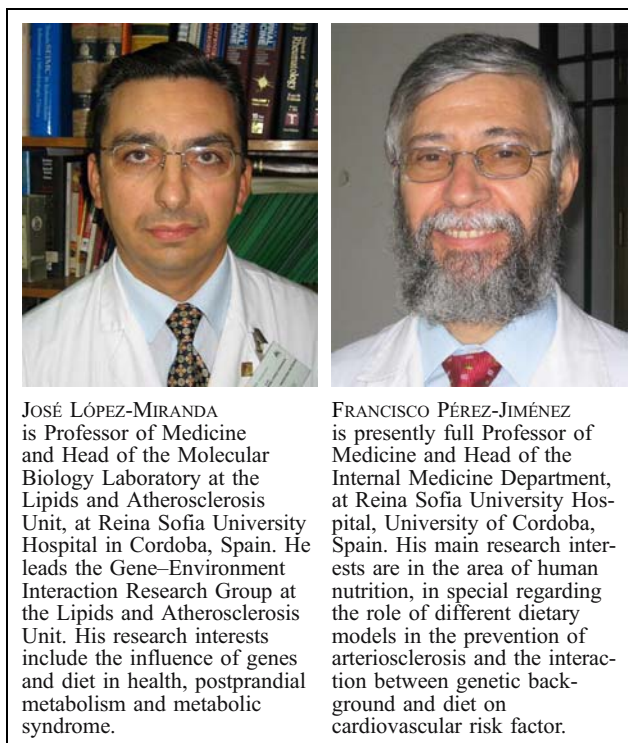
## Dietary fat, genes and insulin sensitivity

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**Abstract** Both insulin resistance and dyslipidaemia are determined by genetic and environmental factors. Depending on their expression and their function, gene variants may influence either insulin action or dyslipidaemia. The purpose of this review was to give some examples from recent studies of gene variants that influence insulin signalling and the interaction between gene and diet to predispose insulin resistance. Recent findings indicate a major role for genetic susceptibility to the insulin resistance syndrome. Nutrition also plays an important role in the development and progression of the condition. Genetic background may interact with habitual dietary fat composition, affecting predisposition to the insulin resistance syndrome and individual responsiveness to changes in dietary fat intake. Due to the complex nature of gene–environment interactions, therefore, therapeutic dietary therapy may require a ‘personalized’ nutrition approach in the future. Although results have not always been consistent, gene variants that affect primary insulin action or dyslipidaemia, and particularly their interaction with the environment, are important modulators of glucose metabolism and insulin resistance syndrome.

**Keywords** Insulin resistance · Dietary fatty acids · Gene polymorphism · Gene–diet interaction



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### Introduction

Insulin resistance is a characteristic finding in individuals with abnormal glucose tolerance, although even individuals with normal glucose tolerance can also be insulin resistant [1]. Insulin resistance means that circulating insulin does not have its normal function in insulin-sensitive tissues, for example skeletal muscle, adipose tissue, liver and endothe-

lium [2]. Insulin resistance is usually accompanied by a compensatory increase in insulin secretion from the pancreas to overcome impaired insulin action in peripheral tissues to maintain the glucose level within the normal range.

Insulin resistance is not only related to glucose metabolism, but is also associated with obesity, central obesity, elevated blood pressure, elevated levels of triglycerides, low levels of high-density lipoprotein (HDL) cholesterol and haemostatic abnormalities (Fig. 1). This clustering of cardiovascular risk factors, called the metabolic syndrome [3, 4], predicts cardiovascular disease not only in non-diabetic individuals [5] but also in middle-aged and elderly patients with type 2 diabetes mellitus (T2DM) [6].

Insulin resistance clusters in families and is determined by genetic and environmental factors. The genetic component can be estimated by heritability, which is that proportion of the phenotypic variance that is attributed to the additive effects of genes. The heritability of insulin sensitivity, evaluated by the minimal model technique, has been relatively constant, in the 30–40% range [7]. However, heritability estimates vary depending on the method used to evaluate insulin sensitivity.

#### Nutrient determinants of the insulin resistance

Many aspects of the diet composition have been considered to be important in the modulation of insulin resistance, but during the past few years, more attention has been paid to the ability of the type of dietary fat, independent of the total amount, to influence insulin sensitivity and thus, the risk of T2DM. The American Diabetes Association thus recommends a saturated fat intake of <7% of total calories, minimal intake of trans fat and a cholesterol intake of <200 mg per day for individuals with diabetes, plus carbohydrate monitoring to regulate blood glucose [8], whereas the American Heart Association recommends patients with metabolic syndrome to improve their weight control and reduce their total calorie intake. The diet should be low in saturated fats, trans fats, cholesterol, sodium and simple sugars. In addition, there should be ample intakes of fruits, vegetables and whole grains, and the consumption of fish should be encouraged [9]. As far as identifying successful dietary interventions to improve insulin sensitivity is concerned, the most obvious treatment would be to reduce adipose tissue mass [10]. However, poor compliance means that this therapeutic approach is usually ineffective, and the prevalence of obesity continues to rise. Other strategies to attenuate the impact of insulin resistance in the presence of obesity are therefore required. There is a considerable amount of evidence to suggest that dietary fat composition affects insulin resistance [11]. A prospective study demonstrated an important relationship between

serum fatty acid composition, a biomarker of habitual dietary fat intake, and the development of T2DM [12]. Baseline serum saturated fatty acids (SFA) levels rose and polyunsaturated fatty acids (PUFA) decreased in middle-aged normoglycaemic men who developed insulin resistance in the subsequent 4 years. Dietary intervention studies have demonstrated that substituting SFA for monounsaturated fatty acids (MUFA) alters plasma fatty acids composition and improves insulin sensitivity. In agreement with this, our group has demonstrated that in healthy people, the isocaloric substitution of MUFA for SFA improved insulin sensitivity *in vivo* and *in vitro*, with an increase in glucose disposal [13]. Moreover, in the KANWU study, Vessby et al. [14] showed that a change in the proportions of dietary fatty acid, decreasing SFA and increasing MUFA, improves insulin sensitivity but has no effect on insulin secretion in healthy subjects. It is interesting to note that fatty acid composition also has an immediate effect on insulin sensitivity. Thus, an alternative explanation for the decrease in insulin requirements, with MUFA diets, is a reduction in glucose availability and consequently, in the need for insulin. A SFA-rich lipid infusion significantly reduced the insulin sensitivity index (40–50%) to a much greater extent than a PUFA-rich lipid infusion (20–27%) [15]. Thus, PUFA are another potential substitute for SFA [16]. In a study performed on hyperlipemic patients, a diet rich in PUFA (PUFA/SFA ratio of 2) was shown to induce more favourable glucose tolerance than a diet high in SFA (PUFA/SFA ratio of 0.2), especially in hypertriglyceridemic subjects [17]. Some prospective studies have attempted to evaluate the relationship between the consumption of n-3 PUFA or, more generally, of fish, and the risk of diabetes [18, 19]. Three studies demonstrated a beneficial effect of a higher intake on the risk of diabetes or impaired glucose tolerance, whereas one did not. In contrast, short-term diet intervention studies in subjects with and without T2DM have shown that there is no effect of n-3 PUFA on insulin sensitivity. Longer-term intervention studies are scarce, but they too have failed to show significant improvements in insulin sensitivity in healthy and diabetic patients [20]. To summarize, several studies using diets high in PUFA have provided conflicting conclusions on the effect of these compounds on glucose metabolism (Table 1).

On the other hand, it has been suggested that the effects of n-6 PUFA on glucose metabolism may share more similarities with the effects of MUFA [11]. All in all, 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.

The mechanisms linking dietary fat quality to insulin sensitivity are not fully understood. However, the effects of

**Table 1** Effect of diet composition on insulin sensitivity in dietary studies

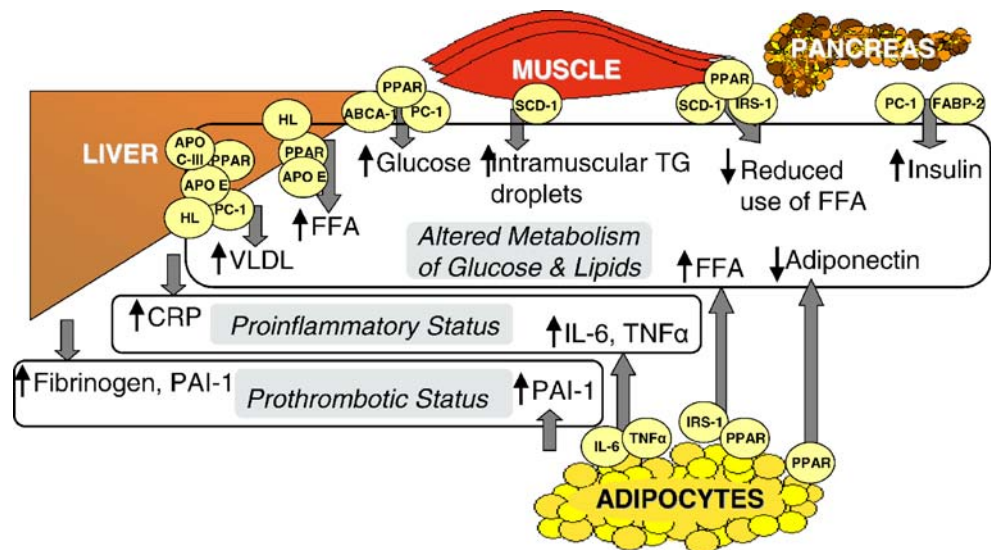
Study	Population	Study design	Conclusion
Laaksonen et al. [12]	Middle-aged normoglycaemic men (n=895)	Prospective cohort study was followed up after 4 years	High content of serum linoleate decreased the risk of developing impaired fasting glycaemia or diabetes mellitus in middle-aged men over a 4-year follow-up, possibly mediated in part by insulin resistance
Perez-Jimenez et al. [13]	59 young subjects (30 men and 29 women)	Dietary study with a saturated fat phase and two randomized-crossover dietary periods: a high-carbohydrate diet and a Mediterranean diet for 28 days each	Iso-caloric substitution of carbohydrates and monounsaturated fatty acids for saturated fatty acids improved insulin sensitivity in vivo and in vitro, with an increase in glucose disposal
Vessby et al. [14]	162 healthy subjects	Random and controlled isoenergetic diet for 3 months, high proportion of SFA or MUFA diet. There was a second assignment at random to supplements with fish oil (3.6 g n-3 fatty acids/day) or placebo	A change in the proportions of dietary fatty acids, decreasing SFA and increasing MUFA, improves insulin sensitivity but has no effect on insulin secretion. The addition of n-3 fatty acids influenced neither insulin sensitivity nor insulin secretion
Feskens et al. [19]	175 men and women aged 64–87 years who were normoglycemic and free of clinical diabetes	Retrospective cohort. Sixty percent of the subjects usually ate fish, with a mean daily intake of 24.2 g	In an elderly population, the habitual consumption of a small amount of fish may protect against the development of impaired glucose tolerance and diabetes mellitus
Rivellese et al. [20]	16 patients with diabetes type 2 and hypertriglyceridemia	Randomized double-blind placebo-controlled design with a parallel group sequence. Subjects were assigned to either fish oil (2.7 g/day eicosapentaenoic plus docosahexaenoic acid for 2 months, then 1.7 g/day for 4 more months) (n=8) or placebo (n=8)	Omega-3 fatty acids did not improve insulin sensitivity. However, moderate amounts of fish oil induce a long-term significant reduction in plasma triglycerides, VLDL triglycerides and NEFA, without deteriorating blood glucose control

*PUFA* Polyunsaturated fatty acids; *MUFA* monounsaturated fatty acids; *SFA* saturated fatty acids; *NEFA* non-esterified fatty acid; *VLDL* very low density lipoproteins

dietary fatty acids on this biological function are believed to be mediated, at least partially, through the fatty acid composition of cell membranes. A specific cell membrane fatty acids profile might influence insulin action via several potential mechanisms, including altered insulin receptor affinity binding, and by influencing ion permeability and

cell signalling. Cross-sectional data suggest that insulin-resistant states are associated with high stearoyl-CoA desaturase (SCD-1) and delta 6-desaturase (D6D) activity, and low delta 5-desaturase (D5D) activity [21]. In a prospective study, Warensjo et al. [22] evaluated serum cholesteryl ester fatty acid composition and estimated

**Fig. 1** Alterations present in insulin resistance



SCD-1, D6D and D5D activities as precursors to fatty acid ratios. The study showed that baseline fatty acid profiles predicted the development of the metabolic syndrome 20 years later, SFA levels were significantly higher and linoleic acid levels were lower in subjects who subsequently developed metabolic syndrome by age 70. SCD-1 and D6D activities were also significantly higher and D5D activity lower in those who developed metabolic syndrome during follow-up. The clinical relevance of altered desaturase activity requires further study. Interestingly, lacking the SCD-1 gene has improved insulin sensitivity, lipid metabolism and resistance to diet-induced weight gain [23]. A recent study has also shown that SCD-1 expression was up-regulated in the skeletal muscle of obese, insulin-resistant subjects, and that this was associated with partitioning of fatty acid metabolism toward storage and away from oxidation [24]. Interestingly, this study suggested that elevated SCD-1 expression and abnormal lipid partitioning might be driven by epigenetic factors, as these characteristics were retained in primary skeletal myocytes derived from obese subjects. This observation raises the possibility that defects in fatty acid metabolism may be acquired as a result of genetic imprinting. The importance of epigenetic phenomena, whereby adverse nutrition/metabolic exposures alter gene activity states not conferred by variations in DNA sequence is being increasingly widely recognized [25, 26]. Thus, obesity-induced changes in DNA methylation and/or histone modification provoke irreversible perturbations in SCD1 gene regulation, which in turn affect fatty acid metabolism. Clearly disturbed fatty acid metabolism, which may be secondary to excessive/imbalanced dietary fat intake, may be involved in the pathogenesis of insulin resistance.

In conclusion, there is evidence from studies on humans to indicate that the quality of dietary fat is capable of influencing insulin sensitivity as well as the other metabolic abnormalities linked with insulin resistance. However, the effects are not always interrelated, suggesting that there are several mechanisms of action. New intervention studies are urgently required to evaluate the clinical benefits of an appropriate nutritional approach to the prevention of insulin resistance.

### Genetic determinants of insulin resistance

Genes and the environment determine insulin resistance. In skeletal muscle, insulin resistance leads to lower rates of glucose uptake, whereas in the liver, it leads to higher rates of hepatic glucose production mainly as a result of increased gluconeogenesis, but also of dyslipidaemia, because a higher flux of portal free fatty acids (FFAs) leads to an increase in the synthesis of very low density

lipoprotein (VLDL) particles, resulting in elevated levels of total and VLDL triglycerides [27]. Low levels of HDL-cholesterol could be at least partly a consequence of elevated triglyceride levels, but other mechanisms are also involved because many insulin-resistant individuals have normal triglyceride levels. Insulin resistance is also often associated with small and dense low-density lipoprotein (LDL) particles. Insulin resistance in adipose tissue, particularly an impairment in the antilipolytic effect of insulin, leads to increased release of FFAs, which are used by the liver for gluconeogenesis and triglyceride synthesis [27]. High concentrations of FFAs can block glucose oxidation, impair glucose transport and lead to impaired glucose metabolism.

This cascade of events is potentially affected by variants (polymorphisms, mutations) in genes regulating insulin action in different tissues. A 'thrifty genotype hypothesis' implies that the evolutionary selection of genes that were originally beneficial for energy storage may be harmful in the setting of a modern environment of physical inactivity and an excessive energy intake. These genes are included in both glucose and lipid metabolism. If the genes of interest are only expressed or play their major role in skeletal muscle or endothelium, it is not very likely that they will induce dyslipidaemia. However, if the variants play an important role in liver and fat tissue, they are likely to influence both glucose and lipid metabolism. Another possibility is that the genes of interest regulate lipids and lipoproteins, and their effects could thus primarily lead to dyslipidaemia [28]. Several previous population-based studies have shown that high levels of triglycerides and low levels of HDL-cholesterol and small, dense LDL, also predict T2DM. Therefore, genes that primarily regulate lipid and lipoprotein levels can secondarily lead to insulin resistance in all target tissues, and finally to impaired glucose metabolism such as lipoprotein lipase [29]; apolipoprotein A5 [30]; hepatic lipase (HL) [31–33]; ATP-binding cassette, sub-family G, member 5 (ABCG5); ATP-binding cassette, sub-family G, member 8 (ABCG8) [34]; the transcription factor sterol regulatory element binding protein [35]; fatty acid transport protein-4 [36]; SCD-1 [37] and microsomal triglyceride transfer protein gene [38]. Both of these possible alternatives must therefore be considered in evaluating the role of genes interacting with glucose and lipid metabolism.

Recent studies in patients with insulin resistance and diabetes have demonstrated that the risk of T2DM and insulin resistance can be influenced by polymorphisms in a number of genes. These include the genes for the peroxisome-proliferator-activated receptor  $\gamma$  (PPAR $\gamma$ ), a nuclear receptor involved in insulin action; Kir6.2, an inward rectifying potassium channel that regulates insulin secretion [39]; calpain 10, a ubiquitously expressed

cysteine protease; the hepatocyte nuclear factor 4 $\alpha$  (HNF-4 $\alpha$ ) [40], a transcription factor that regulates pancreatic beta-cell function; and most recently, transcription factor 7-like 2 (TCF7L2), a transcription factor that regulates the expression of proglucagon genes in enteroendocrine cells by affecting the Wnt signalling pathway [41]. Genetic variation at each of these loci alters the risk of diabetes by approximately 15 to 20%, although the contribution of TCF7L2 appears to be greater [41]. Unfortunately, it is not yet clear how these diverse genetic risk factors interact with one another or with environmental factors to alter susceptibility to T2DM. Furthermore, six genes account for the majority of the 34 monogenic forms of diabetes: HNF-4 $\alpha$ , glucokinase (GCK), hepatic nuclear factor 1 $\alpha$  (HNF-1 $\alpha$ ), insulin promoter factor-1 (IPF-1), hepatic nuclear factor 1 $\beta$  (HNF-1 $\beta$ ) and neuro D1 transcription factor (NEUROD1) [42].

In addition, candidate gene association studies in T2DM and insulin resistance indicate a role for a number of genes involved in insulin action as well as  $\beta$ -cell function, including insulin, insulin receptor, PI3 kinase, regulatory subunit, polypeptide 1 (p85 alpha), potassium channel inwardly rectifying subfamily J, member 11 (KCNJ11), glucose transporter 2 (GLUT-2) [43], TRB3, a mammalian tribbles homolog [44], insulin-degrading enzyme and protein tyrosine phosphatase 1B (PTB1B) [45–48]. Several components of the insulin signalling cascade are impaired in skeletal muscle from patients with T2DM, including tyrosine phosphorylation of insulin receptor 1 (IRS-1) and the activity of phosphatidylinositol-3-kinase (PI3K) [49, 50], AMP-activated protein kinase [51] and protein kinase B (PKB) [52, 53]. Furthermore, several genes involved in adipocyte metabolism are involved in insulin resistance. These include leptin [54], leptin receptor [55, 56], beta2- and beta3-adrenergic receptors [57, 58], adiponectin [59–61], adiponectin receptors [62–64], resistin [65, 66], uncoupling protein 2 [67, 68] and perilipin [69].

Fasting hyperglycaemia in T2DM is associated with lack of inhibition of two key gluconeogenic enzymes, phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase). Insulin inhibits the expression of these enzymes at the transcriptional level through PKB [70]. The essential role of PKB $\beta$  (or AKT2) in insulin signalling and the maintenance of glucose homeostasis have recently been demonstrated by the finding of a missense mutation in AKT2 in a family with severe insulin resistance and diabetes [71]. PKB also regulates peroxisome proliferator-activated receptor  $\gamma$  (PPAR $\gamma$ ) coactivator (PGC1) [72], the transcriptional coactivator that interacts with hepatic nuclear factor 4 $\alpha$  (HNF4 $\alpha$ ), PPAR $\gamma$  and forkhead transcription factor 1 (Foxo1) to execute hepatic gluconeogenesis.

Another promising locus is the ATP-binding cassette A1 (ABCA1) transporter, which is involved in the cholesterol

efflux from macrophages to HDL. In addition to Tangier disease, a defective ABCA1 gene has been associated with lower HDL cholesterol and higher CVD risk. Recent evidence suggests that there are further associations with insulin resistance, as demonstrated by the relation between ABCA1 gene expression and fasting glucose concentration in vivo [73].

To summarize, several genes regulate insulin action, and a complete review of these findings is not possible in this review. Therefore, the following paragraphs only offer some examples, including genes that regulate insulin receptor function (PC-1), early insulin signalling (insulin receptor substrates), fatty acid binding protein type 2, nuclear receptors (PPAR-g2) and the inflammatory response (IL-6).

#### PC-1

The class II transmembrane glycoprotein PC-1 is a potential candidate gene for insulin resistance and T2DM because it inhibits insulin receptor tyrosine kinase activity. The K121Q polymorphism in exon 4 of the PC-1 gene has been associated with insulin resistance and hyperglycaemia in many [74], but not all studies [75]. Some studies [76] have shown that the K121Q polymorphism is correlated with insulin sensitivity independently of obesity. Much less information is available on the effect of the K121Q polymorphism on lipids and lipoproteins. In the study by Kubaszek et al. [77], the K121Q polymorphism was associated with insulin resistance, but not with dyslipidaemia in Finns. In contrast, in the study by Gonzales-Sanchez et al. [78], the K121Q polymorphism was associated with high plasma leptin and triglyceride levels.

#### Insulin receptor substrates

Insulin receptor substrate (IRS) type 1 is a major substrate for the insulin receptor and regulates insulin signalling in skeletal muscle, adipose tissue and the vasculature, making it a promising candidate gene for insulin resistance [79] and T2DM. The most common variant in the IRS-1 gene is the Gly972Arg substitution, which causes an impairment in IRS-1-associated phosphatidylinositol 3-kinase activity [80]. A recent study by Marini et al. [81] showed that insulin sensitivity, as assessed by the hyperinsulinaemic clamp technique, was significantly reduced in carriers of the Gly972Arg variant compared with carriers of the common genotype. Furthermore, carriers of this polymorphism had several features of the metabolic syndrome, including high levels of total triglycerides, total/HDL-cholesterol ratio, FFA levels, systolic blood pressure and intima-media thickness. These results are in line with a previous report showing that carriers of the Gly972Arg substitution had a significantly higher body mass index, fasting insulin, insulin resistance and plasma triglyceride

levels than obese non-carriers [82]. The Gly972Arg polymorphism in the IRS-1 gene thus seems to be associated with the insulin resistance and dyslipidaemia often present in the metabolic syndrome. IRS-2 is also a key mediator in insulin signalling. IRS-2 knockout mice exhibited impaired insulin secretion, insulin resistance and abnormal glucose tolerance, a phenotype similar to human T2DM [83]. However, mutations in this gene do not seem to be responsible for T2DM in humans. The Gly1057Asp polymorphism has been widely studied in several populations, but it is not responsible for impaired insulin secretion, impaired insulin action or T2DM [84]. A recent meta-analysis was unable to replicate the association of the IRS-1 Gly972Arg polymorphism with T2DM [85].

### PPAR- $\gamma$

A nuclear receptor, peroxisome proliferator-activated receptor gamma (PPAR- $\gamma$ ), is widely expressed in adipose tissue and regulates adipocyte differentiation, body weight and glucose homeostasis. Mutations in this gene might therefore affect insulin sensitivity and lipid metabolism. In fact, rare mutations in the PPAR- $\gamma$  gene have yielded important information. Loss-of-function mutations result in lipodystrophy, and gain-of-function mutations increase body fat mass [86]. Further evidence about the role of PPARs in the liver, adipose tissue and skeletal muscle comes from the use of PPAR- $\alpha$  and PPAR- $\gamma$  agonists, thiazolidinediones, which lower both glucose and triglyceride levels and elevate the level of HDL-cholesterol [86]. Thiazolidinediones improve glycemic control and insulin sensitivity in patients with type 2 diabetes, despite their potential to cause weight gain. Studies have attempted to elucidate the mechanisms behind the apparent paradox of thiazolidinediones improving insulin sensitivity while causing weight gain. Data indicate that thiazolidinedione treatment produces a favourable shift in fat distribution from visceral to subcutaneous adipose depots that is associated with improvements in hepatic and peripheral tissue sensitivity to insulin [87].

Deeb et al. [88] reported a Pro12Ala polymorphism in exon B of this gene, finding that the Pro12Ala substitution was associated with low body weight (and body mass index), high insulin sensitivity and a high HDL-cholesterol level and a low total triglyceride level. In the same study, the Pro12Pro genotype was more common in second-generation Japanese–American men with diabetes than in non-diabetic men. Several recent studies have confirmed that the Pro12Pro genotype is associated with T2DM and insulin resistance, and it is currently probably the most promising gene of susceptibility for T2DM [89–92]. Lindi et al. [93] recently reported that the Pro12Ala polymorphism of the PPAR- $\gamma$ 2 gene regulated conversion to T2DM in the Finnish

Diabetes Prevention Study. Interestingly, they also noted that the regulation of insulin sensitivity by the Pro12Ala polymorphism in adult life is dependent on body size at birth [94]. In low birth-weight subjects, the Pro12Pro genotype was associated with increased insulin resistance and elevated insulin concentrations. Recent studies have also shown that the X12Ala variant is significantly associated with greater insulin sensitivity [95–97]. Although it seems to be clear that the PPAR- $\gamma$ 2 gene regulates lipid metabolism, the results of several studies are inconsistent, and it is difficult to draw any solid conclusions [98, 99].

The Pro12Ala polymorphism of the PPAR- $\gamma$ 2 gene may interact with other genes that regulate the insulin signalling pathway. The study by Baratta et al. [100] demonstrated a significant interaction of the Pro12Ala polymorphism and the K121Q polymorphism of PC-1. Among carriers of the Pro12Pro genotype, individuals with the X121Q genotype of PC-1 had a significantly higher fasting plasma glucose level and insulin area under the curve in the oral glucose tolerance test and significantly lower insulin sensitivity than the K121K carriers of the PC-1 gene. Fatty acid binding protein4-376 and PPAR- $\gamma$  Pro12Ala polymorphisms also interactively influence insulin sensitivity and body composition in nondiabetic, Hispanic and non-Hispanic white males [101].

Peroxisome proliferator-activated receptor gamma coactivator 1 alpha (PGC-1alpha) is a transcriptional coactivator implicated in insulin release by beta cells and in insulin resistance. A recent study suggests that PPARGC1A promoter polymorphisms are associated with age at diagnosis of T2DM and early-onset T2DM in the Korean population [102].

### Fatty acid binding protein type 2

The intestinal fatty acid binding protein (FABP) type 2 gene belongs to a family of more than 20 FABP genes and is expressed only in absorptive columnar epithelial cells of the small intestine. FABP-2 transports hydrophobic fatty acids from the plasma membrane to the endoplasmic reticulum where FFA are used to form triglycerides [103]. The common polymorphism, Ala54Thr, has been identified in the FABP-2 gene [104], which could be associated with insulin resistance, as elevated dietary fat absorption leads to high levels of circulating FFA and an increase in plasma triglyceride concentrations.

The study by Baier et al. [104] in Pima Indians showed that the 54Thr allele was associated with a high fasting insulin level, lower rates of insulin-mediated glucose uptake and higher rates of fat oxidation *in vivo*, as evaluated by the euglycaemic hyperinsulinaemic clamp technique. Several other studies following this original observation on the effect of the Ala54Thr polymorphism on insulin sensitivity have been published, but the results have been quite conflicting. Galluzzi et al. [105] showed that the

Ala54Thr polymorphism was associated with 2-h postchallenge insulin levels in the Framingham Offspring Study. There was no evidence to suggest that the Ala54Thr polymorphism could contribute to an elevated risk of T2DM on the basis of ten different studies [103].

#### IL-6, IL-10 and TNF-alpha

Interleukin-6 (IL-6) is a pleiotropic cytokine that regulates the immune response, the acute-phase response, hematopoiesis and body energy balance. Genetic polymorphism at the -174 position of the IL-6 promoter has recently been reported to be linked with insulin resistance [106–108], although the results have been conflicting [109, 110]. IL-10 is a major anti-inflammatory cytokine that has been associated with obesity and T2DM. A recent study suggests that polymorphisms and haplotypes of the IL-10 promoter may be associated with obesity and insulin resistance in a large sample of Italian Caucasians [111].

Variation in the tumour necrosis factor gene (TNF) has been associated with insulin resistance traits [112, 113]. Data from a recent meta-analysis indicate that individuals who carried the -308A TNF-alpha gene variant are at a 23% greater risk of developing obesity than controls and that they displayed significantly higher systolic arterial blood pressure and plasma insulin levels [114], supporting the hypothesis that the TNF-alpha gene is involved in the pathogenesis of the metabolic syndrome.

#### Genetic determinants of dietary responsiveness

It is well known that the effect of dietary changes on plasma biomarker concentrations differs significantly between individuals. This topic has been extensively studied for plasma lipid concentrations and recently for insulin sensitivity (Table 2). Some individuals appear to be relatively insensitive (hypo-responders) to dietary intervention, whereas others (hyper-responders) have an enhanced sensitivity. Therefore, it is clear that what is good at population level is not necessarily good at individual level. Moreover, there is increasing evidence that supports the concept that this variability in response is an intrinsic characteristic of the individual, rather than being the result of different dietary compliance with the experimental protocols. Currently, there is considerable support for the notion that interindividual variability in response to dietary modification is influenced by genetic factors, especially for lipid and lipoprotein phenotypes [115]. However, the complexity associated with the interpretation of the current data represents only the tip of the iceberg of the full complexity of the potential interactions between genes, diet and insulin resistance considered as a whole. In this regard,

a few genes have already been explored in terms of gene–diet interactions, which modulate the expression of the insulin resistance syndrome or certain of its components.

The concept of gene–diet interaction describes the modulation of the effect of a dietary component on a specific phenotype (plasma lipid concentrations, insulin resistance, glycaemia, etc.) by a genetic polymorphism. Alternatively, this notion refers to the dietary modification of the effect of a genetic variant on a phenotypic trait. In terms of gene–diet interactions for common, multifactorial diseases, the most rapid development has been in the area of risk of cardiovascular disease, which has easily measured risk factors (i.e. plasma cholesterol concentrations and insulin resistance). The potential benefits of harnessing the power of genomics for the dietary prevention of disease are enormous, and this approach is considered to be the future of nutritional research in the postgenomics era [116]. The genomics revolution has catapulted the development of several new technologies that can be applied in nutritional sciences [117]. Genomic, proteomic, metabonomic and bioinformatic techniques are already beginning to facilitate the study of gene–nutrient interactions at cell, individual and population level [118]. During this postgenomics era, traditional DNA sequencing and genotyping technologies will shift towards novel approaches using DNA arrays and other high-throughput techniques [119]. All of these techniques can and should be used in combination to improve our understanding the influence of both specific nutrients and whole dietary patterns on the metabolic behavior of cells, organs and the whole organism [120].

It is important to consider the dynamic nature of these interactions throughout the life span. First, fetal development and *in utero* conditions would be essential to produce the first gene–nutrient interactions. Secondly, under certain conditions, as in the case of inborn errors of metabolism, nutrition in the first years of life is a key determinant of health or disease status. Third, for multifactorial diseases such as atherosclerosis, cardiovascular risk factors (plasma lipid concentrations, insulin resistance, glycaemia, etc.) and cancer, a long period of exposure to the same dietary pattern would be necessary to develop the disease phenotype.

Apolipoprotein E (apoE) is a structural component of several lipoproteins and serves as a ligand for the LDL receptor and the LDL receptor-related protein. The apoE gene promoter 219G/T polymorphism is associated with coronary heart disease and increased postprandial triacylglycerol-rich lipoprotein concentration [121] and LDL susceptibility to oxidative modifications [122], circumstances related to insulin resistance. We investigated the effect of this polymorphism on peripheral insulin sensitivity using the insulin suppression test after the consumption of three diets: high MUFA, high SFA and high carbohydrate (CHO) diet. The steady-state plasma glucose (SSPG) concentration was

**Table 2** Genetic determinants of dietary responsiveness in insulin resistance

Gene polymorphism	Population	Dietary factors	Conclusion
apoE gene -219G/T polymorphism [123]	<i>n</i> =43 with the apoE3/E3 genotype (8 GG, 25 GT and 10 TT)	Three dietary periods, each lasting 4 weeks: high SFA, high MUFA and low fat, high carbohydrate	Carriers of the -219T allele are less insulin-sensitive than GG individuals. Furthermore, only carriers of the -219G allele have improved IS when MUFA- or CHO-rich diets are consumed instead of a SFA-rich diet
Apolipoprotein CIII T-455C polymorphism in the insulin-responsive element [131]	848 heart disease patients	Erythrocyte n-3 PUFAs as suitable markers of dietary intake of fatty acids	Patients homozygous for the -455C APOC3 variant are poorly responsive to the apo C-III-lowering effects of n-3 PUFA
FABP2 Ala54Thr polymorphism [127]	28 Ala54/Ala54, 27 Ala54/Thr54, and 4 Thr54/Thr54	Three dietary periods, each lasting 4 weeks: high SFA, high MUFA and low fat, high carbohydrate	Steady state plasma glucose concentrations were significantly higher in Ala54Thr subjects after the SFA diet than after the CHO diet or the Mediterranean diet. However, no significant differences among the 3 diets were observed in the Ala54 allele homozygotes
Hepatic lipase -514 C/T polymorphism [128]	39 homozygous (C/C) and 20 carriers of the T allele (CT/TT)	Three dietary periods, each lasting 4 weeks: high SFA, high MUFA and low fat, high carbohydrate	The results show an improvement in insulin sensitivity in men with the -514T allele of the HL promoter polymorphism, when MUFA and carbohydrates are consumed instead of SFA fat
Scavenger receptor class B type I (SR-B1) exon I (G->A) polymorphism [130]	42 GG homozygous and 17 GA heterozygous	Three dietary periods, each lasting four weeks: high SFA, high MUFA, and low fat, high carbohydrate	Carriers of the G/A genotype have significant increases in insulin sensitivity after a MUFA-rich diet compared to G/G individuals
Nitric oxide [132]	eNOS(+/-) partial deletion mice	High fat diet vs normal diet	When fed a normal diet, these mice had normal insulin sensitivity and were normotensive. When fed a high-fat diet, however, eNOS(+/-) mice developed exaggerated arterial hypertension and had fasting hyperinsulinemia and a 35% lower insulin-stimulated glucose utilization than control mice
Peroxisome proliferator-activated receptor alpha (PPARalpha) leucine to valine (L162V) [133]	1,003 men and 1,103 women in the Framingham Cohort	Consuming their habitual diets	The effect of the L162V polymorphism on plasma TG and apoC-III concentrations depends on the dietary PUFA, with a high intake triggering lower TG in carriers of the 162V allele

lower in GG subjects than in GT and TT individuals, regardless of the diet consumed. Significant diet by genotype interactions were found for SSPG and plasma FFA concentrations. Thus, the shift from the SFA-rich diet to the MUFA- or CHO-rich diets decreased the SSPG and FFA concentrations in GG and GT, but not in TT subjects [123].

The intestinal fatty acid-binding protein coded by the FABP2 gene is one of the most abundant proteins in enterocytes, and genetic variation at this locus was associated with insulin resistance in Pima Indians. A polymorphism in FABP2 that results in an alanine-to-threonine substitution at amino acid 54 of the intestinal fatty acid-binding protein has been associated with hypertriglyceridemia, insulin resistance [124, 125] and the risk of diabetes type 2 [126]. In a recent study [127], we showed that insulin sensitivity was reduced in subjects with the Thr54 allele of the FABP2 polymorphism when SFA were

replaced by MUFA and carbohydrates. However, no significant differences among the three diets were observed in the Ala54 allele homozygote.

Human HL is a lipolytic enzyme that plays a role in the metabolism of several lipoproteins, whereas insulin up-regulates the activity of HL via insulin-responsive elements in the HL promoter. We have examined the influence of -514 C/T polymorphism in the promoter of this gene on insulin sensitivity in 59 healthy young subjects (30 men and 29 women). SSPG concentrations (a measure of insulin sensitivity) were significantly higher in male carriers of the -514T allele after the consumption of the SFA diet than after the CHO diet and the Mediterranean diet. This effect was not observed in women. Moreover, there were no significant differences in insulin sensitivity after the three diets in men and women with the CC genotype [128]. Furthermore, the -514C>T polymorphism of the LH gene is associated with higher liver fat content and lower whole-

body insulin sensitivity in a cross-sectional study with 1,070 normal subjects [33].

Scavenger receptor class B type I (SR-B1) mediates the absorption of dietary cholesterol in the intestine, suggesting that it also plays a role in postprandial responses. The presence of the two alleles at the SR-B1 polymorphism in exon 1 was associated with faster clearance of small-TRLs, probably related to a more rapid hepatic uptake [129]. Increasing evidence indicates that (SR-B1) plays additional roles, particularly in T2DM. In a recent study, we showed that carriers of the G/A genotype display significant increases in insulin sensitivity after a MUFA-rich diet compared to G/G individuals [130].

Apolipoprotein CIII (apo CIII) is a marker of cardiovascular disease risk associated with triglyceride-rich lipoproteins. The T-455C polymorphism in the insulin-responsive element of the apo CIII gene influences triglyceride and apo CIII concentrations. A formal interactive effect between apo CIII genotype and n-3 PUFA was confirmed by logistic models in the study of Oliveri et al. [131]. Patients homozygous for the -455C APOC3 variant are poorly responsive to the apo C-III-lowering effects of n-3 PUFA.

Nitric oxide (NO) plays a major role in the regulation of cardiovascular and metabolic homeostasis, as evidenced by insulin resistance and arterial hypertension in endothelial NO synthase-null mice. Although extrapolation of these findings to humans is difficult, partial gene deletion of endothelial nitric oxide synthase predisposes to exaggerated high-fat, diet-induced insulin resistance and arterial hypertension [132].

Finally, the list of genes includes two members of the PPAR family of nuclear transcription factors. Considering the involvement of these factors in the regulation of multiple genes involved in the different metabolic pathways associated with the insulin resistance syndrome, the important role played by these genes and diet in the expression of the disease and/or associated phenotypes comes as no surprise. In a recent study, Tai et al. [133] showed that the effect of the L162V polymorphism on plasma triglyceride and apo C-III concentrations depends on the dietary PUFA, with a high intake triggering lower triglyceride in carriers of the 162V allele. In addition, the PPAR $\alpha$  Leu162Val polymorphism may contribute to interindividual variability in plasma lipoprotein and lipid response after modification of the dietary PUFA/SFA ratio [134].

## Conclusions

The insulin resistance syndrome comprises a set of metabolic and physiological risk factors that are associated with an elevated risk of cardiovascular disease. The expression of each of its major factors (hypertriglyceridemia, low high-density

lipoprotein cholesterol levels, hypertension, abdominal obesity and insulin resistance) has been found to be the result of complex interactions between genetic and environmental factors. Moreover, diet may play a major role in triggering the insulin resistance syndrome by interacting with genetic variants at candidate genes for dyslipidemia and insulin resistance. In support of this hypothesis, a number of studies of several candidate genes have already demonstrated the significance of these interactions; however, the amount and reliability of the data are still very limited, and in many cases, replication studies are still lacking. Therefore, more studies with better epidemiological design and diet interventions and measures are needed to estimate the relative contributions of diet and genetic predisposition to the insulin resistance syndrome, which is the most common cardiovascular disease risk factor in industrialized societies.

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