


Review

# Regulation of Macronutrients in Insulin Resistance and Glucose Homeostasis during Type 2 Diabetes Mellitus

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**Abstract:** Insulin resistance is an important feature of metabolic syndrome and a precursor of type 2 diabetes mellitus (T2DM). Overnutrition-induced obesity is a major risk factor for the development of insulin resistance and T2DM. The intake of macronutrients plays a key role in maintaining energy balance. The components of macronutrients distinctly regulate insulin sensitivity and glucose homeostasis. Precisely adjusting the beneficial food compound intake is important for the prevention of insulin resistance and T2DM. Here, we reviewed the effects of different components of macronutrients on insulin sensitivity and their underlying mechanisms, including fructose, dietary fiber, saturated and unsaturated fatty acids, and amino acids. Understanding the diet-gene interaction will help us to better uncover the molecular mechanisms of T2DM and promote the application of precision nutrition in practice by integrating multi-omics analysis.

**Keywords:** macronutrients; insulin resistance; glucose homeostasis; type 2 diabetes mellitus

## 1. Introduction

Type 2 diabetes mellitus (T2DM) has become a global health issue that is tightly correlated with the prevalence of obesity and other chronic diseases. T2DM is caused by systemic insulin resistance and impaired insulin secretion in pancreatic  $\beta$ -cells, leading to disorders of carbohydrate, protein, and lipid metabolism [1]. Insulin resistance is a hallmark of prediabetes and gradually contributes to the development of T2DM. Insulin resistance refers to an impaired ability of insulin to lower blood glucose in target tissues at a normal plasma insulin level. Pancreatic  $\beta$ -cells secrete excessive insulin to compensate for the outcome of insulin resistance. Thus, fasting plasma insulin levels rise, and hyperinsulinemia eventually develops [2]. Although it is controversial about the primary defect between insulin resistance and hyperinsulinemia, they together culminate in eventual  $\beta$ -cell failure, resulting in hyperglycemia [3,4].

Insulin receptor (IR) is a tyrosine kinase receptor that is activated upon insulin binding, recruiting downstream substrates such as insulin receptor substrate (IRS). This initiation sets off the proximal insulin signaling pathway. Phosphorylated IRS, in turn, triggers the phosphoinositide 3-kinase (PI3K)  $\rightarrow$  protein kinase B (AKT) signaling cascade, regulating the activity of critical distal downstream targets, including glucose transporter type 4 (GLUT4), mammalian target of rapamycin complex 1 (mTORC1), and forkhead box protein O1 (FoxO1), regulating glucose and energy homeostasis [5,6]. Insulin resistance can manifest at multiple cellular levels, including the desensitization of the insulin receptor at the cell surface, inhibition of IRS function via protein degradation, suppression of PI3K activity, an inability to inhibit FoxO1-induced transcriptional changes, and reduced insulin clearance from the bloodstream [6,7]. Additionally, IR  $\rightarrow$  Carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM1) signaling pathway-mediated hepatic insulin clearance is pivotal for the regulation of insulin homeostasis [7,8]. Impaired insulin clearance leads to progressive insulin resistance, potentially due to the development of chronic hyperinsulinemia.



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Metabolic organs cooperatively respond to nutrient intake and maintain energy balance. The interaction of nutrients, especially macronutrients, with the gastrointestinal tract stimulates the release of incretin hormones such as glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) [9]. GLP-1 improves insulin sensitivity in peripheral tissues through increasing insulin secretion, attenuating inflammation response and endoplasmic reticulum (ER) stress, increasing GLUT-4 expression, and enhancing insulin signal transduction [10–13]. GIP stimulates the release of both insulin and glucagon in the pancreas. Therefore, incretin hormones play a key role in regulating insulin sensitivity and glucose homeostasis. Nutrient ingestion, especially carbohydrates, increases blood glucose and stimulates insulin secretion in the pancreas, thereby suppressing glucose production in the liver, increasing lipogenesis in the adipose tissue, promoting glucose uptake in the skeletal muscle, and regulating glucose homeostasis. Overnutrition-induced obesity is highly related to insulin resistance, primarily through multiple pathological mechanisms. The nutrient-induced GLP-1 secretion is significantly reduced in obese individuals [14,15], which may contribute to systemic insulin resistance. During overnutrition, toxic metabolites including ceramides, diacylglycerol (DAG), and nonesterified fatty acids (NEFA) accumulate and stimulate the activity of protein kinase C (PKC), leading to the Ser/Thr phosphorylation of IR and IRS, thereby impairing insulin sensitivity [2]. Overnutrition elevates branched-chain amino acid levels in the bloodstream, activating mTORC1 and inhibiting IRS function [16]. Proinflammatory cytokine levels in circulation are increased during obesity, which induces Ser/Thr phosphorylation of IRS and inhibits insulin signaling by activating JNK and IKK $\beta$  [17–19]. Hyperinsulinemia associated with obesity leads to insulin resistance by inhibiting the activity of IRS [20]. In this review, we will focus on the effect of macronutrients on insulin resistance and the underlying mechanisms.

## 2. Insulin and Glucagon Action and Insulin Resistance

### 2.1. Molecular Basis of Insulin and Glucagon Signaling

Insulin and glucagon are pivotal hormones that play essential roles in regulating glucose homeostasis. These two hormones cooperate tightly to maintain blood glucose levels within a narrow range, preventing both hyperglycemia and hypoglycemia under certain health conditions. The glucagon-to-insulin ratio is strongly linked to hyperglycemia in patients with type 2 diabetes [21].

Insulin, a peptide hormone secreted from pancreatic  $\beta$ -cells, plays a critical role in orchestrating the anabolic response to nutrient intake, especially the intake of glucose, fatty acids, and amino acids [22]. Insulin regulates blood glucose balance by increasing glucose uptake in skeletal muscle and fat tissues while suppressing hepatic glucose production (HGP). Insulin actions are induced by the intrinsic tyrosine kinase activity of the insulin receptor (IR). Insulin triggers conformational changes and autophosphorylation of IR, leading to the recruitment and phosphorylation of IRS and SH3-containing protein (Shc). IRS activates the PI3K  $\rightarrow$  AKT pathway to govern insulin's metabolic functions, while Shc activates the Ras  $\rightarrow$  MAPK pathway, which mediates growth and differentiation at cellular and organismal levels [23]. Additionally, IR also exerts control over apoptosis, senescence, and the cell cycle, independent of ligand and tyrosine kinase activity [24]. In skeletal muscle and adipose tissues, insulin promotes the translocation of GLUT4 from the cytoplasm to the cell membrane, thereby promoting glucose uptake [25]. Insulin-stimulated GLUT4 trafficking is mediated by the PI3K  $\rightarrow$  AKT  $\rightarrow$  AS160 signaling cascade [26–28]. AS160, a Rab GTPase-activating protein, maintains Rab proteins in an inactive GDP form and results in GLUT4 retention in the cytoplasm. Phosphorylation of AS160 by AKT inactivates its Rab GTPase activity, resulting in an increase in the active GTP form of Rab, thereby promoting GLUT4 trafficking [25,26]. In addition, AKT-induced PIKfyve phosphorylation plays a role in regulating insulin-stimulated GLUT4 trafficking, potentially through PtdIns 3,5-P2 [29–31]. In the liver, insulin inhibits glycogenolysis and gluconeogenesis, thus suppressing glucose release. Insulin activates glycogen synthase by the PI3K  $\rightarrow$  AKT  $\rightarrow$  GSK-3 signaling pathway. AKT stimulates phosphorylation of GSK-3 and inhibits its

kinase activity, thereby dephosphorylating glycogen synthase, stimulating its activity, and promoting glycogen accumulation [32]. The IRS → PI3K → AKT → FoxO1 signaling pathway in the liver is primarily responsible for insulin action on glucose homeostasis [33]. Insulin stimulates phosphorylation of FoxO1 at S253 via the activation of AKT, thereby decreasing FoxO1-induced expression of genes responsible for gluconeogenesis such as *phosphoenolpyruvate carboxykinase 1 (Pck1)* and *glucose-6-phosphatase (G6pase)* and suppressing HGP [34–36]. The central nervous system (CNS), such as the hypothalamus, plays a pivotal role in regulating systemic insulin sensitivity and glucose homeostasis [37]. The activation of insulin signaling in agouti-related peptide (AgRP) but not pro-opiomelanocortin (POMC) neurons suppresses HGP through the hepatic vagal nerve [38]. Insulin induces the hyperpolarization of AgRP neurons and decreases their activity, thus leading to the activation of IL-6-STAT3 signaling and downregulating hepatic gluconeogenic genes, including *Pck1* and *G6pase* [38,39]. Additionally, hypothalamic insulin activation inhibits lipolysis and promotes lipogenesis in white adipose tissue, which may contribute to the central regulation of HGP by limiting the supply of glycerol substrate for gluconeogenesis [40]. In humans, acute intranasal insulin delivery increases systemic insulin sensitivity during hyperinsulinemic-euglycemic clamp and enhances postprandial thermogenesis [41,42]. Chronically daily intranasal insulin administration for 8 weeks decreases body weight and adiposity in healthy men [43]. These results indicate that CNS insulin signaling regulates systemic insulin sensitivity and glucose homeostasis in both humans and mice.

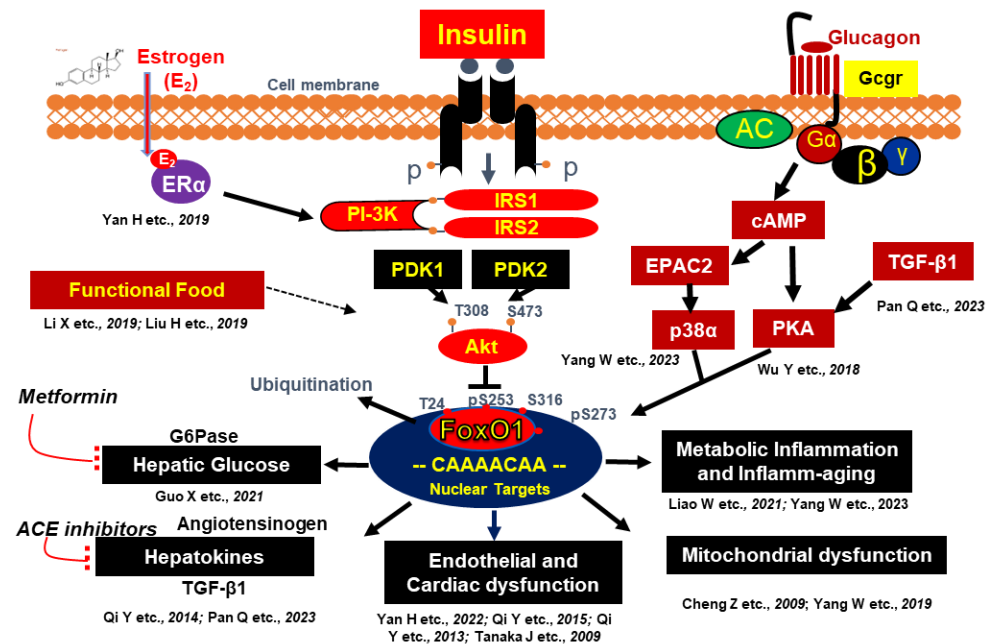
Glucagon is secreted by the pancreatic  $\alpha$ -cells, acting as a catabolic hormone and regulating glucose homeostasis. Glucagon promotes HGP through stimulation of glycogenolysis and gluconeogenesis, thereby maintaining euglycemia under fasting conditions. The action of glucagon is mediated by the glucagon receptor (Gcgr), a G protein-coupled receptor [44]. Upon glucagon binding, Gcgr activates Gs protein, thereby stimulating adenylate cyclase, elevating cyclic adenosine monophosphate (cAMP), and then activating cAMP-dependent protein kinase A (PKA) and exchange protein directly activated by cAMP 2 (EPAC2) [45]. Active PKA, in turn, stimulates the activity of phosphorylase kinase, which then converts glycogen phosphorylase b (PYG b) into the active form PYG a and promotes glycogen breakdown [46]. Glucagon promotes gluconeogenesis through the activation of two key transcriptional factors, cAMP response element-binding protein (CREB) and FoxO1 [47]. Activation of PKA by glucagon induces phosphorylation of CREB at S133, resulting in the formation of the CREB-TORC2 complex and increasing transcription of its downstream gluconeogenic genes, including *Ppargc1a*, *Pck1*, and *G6pase* [48,49]. Glucagon stimulates phosphorylation of FoxO1 at S273 via both PKA and EPAC2 → p38 signaling pathways, enhancing FoxO1 stability and nuclear localization [50,51]. Additionally, glucagon stimulates amino acid uptake and subsequent catabolism, increasing the substrate availability of amino acid metabolites and promoting gluconeogenesis [52]. Hepatic acetyl-CoA allosterically stimulates the activity of pyruvate carboxylase and increases gluconeogenesis in the liver [53]. Glucagon stimulates intrahepatic lipolysis, induces fatty acid oxidation, and increases acetyl-CoA levels, thereby promoting hepatic gluconeogenesis [54]. However, the mediobasal hypothalamus glucagon infusion inhibits HGP through glucagon receptor → PKA signaling [55]. This hypothalamic glucagon action on HGP is mediated by  $K_{ATP}$  channel-dependent mechanisms [56]. These results indicate that there exists a self-regulatory feedback loop to fine-tune glucagon-induced HGP.

## 2.2. The Molecular Basis of Insulin Resistance by Targeting FoxO1

The molecular mechanisms of insulin resistance have been extensively reviewed [2,5,6,23]. During obesity, lipotoxicity, chronic inflammation, hyperglycemia, hyperinsulinemia, mitochondrial dysfunction, and ER stress stimulate the activity of Ser/Thr kinase and impair insulin sensitivity by phosphorylating IR, IRS, and AKT proteins, resulting in insulin resistance. Insulin resistance is a critical mechanism underlying various metabolic disorders. Over the past decade, we have proven that FoxO1 is one of the key factors that link insulin resistance and metabolic disorders. Studies from many labs, including our

own, have demonstrated that FoxO1 promotes HGP by upregulating the expression of gluconeogenic genes, including *Pck1* and *G6pase* [57,58]. Insulin stimulates the activity of AKT and phosphorylates FoxO1 at T24, S253, and S316, thereby suppressing FoxO1 activity and inhibiting HGP [35,36,59,60]. Deletion of liver IRS1 and 2 in mice induces systemic insulin resistance, leading to diabetic symptoms that include hyperglycemia and hyperinsulinemia. Notably, these diabetic symptoms are normalized when hepatic FoxO1 is deficient [33]. We recently uncovered that glucagon stimulates the phosphorylation of FoxO1-S273 through the cAMP → PKA and cAMP → EPAC2 → p38α signaling pathways; this enhances FoxO1 protein stability and promotes its nuclear localization. We also found that FoxO1-S273 phosphorylation prevents insulin-mediated FoxO1 degradation in vitro and impairs glucose tolerance in vivo [50,51]. These findings suggest that FoxO1 is a pivotal mediator connecting glucagon and insulin signaling in the regulation of glucose homeostasis. In addition, FoxO1 plays a crucial role in aging-induced glucose dysregulation and chronic inflammation. We found that the activity of FoxO1 was increased in the livers of old mice. Inhibition of FoxO1 significantly improves glucose homeostasis and attenuates chronic inflammation in Kupffer cells during aging [61]. Activation of FoxO1 impairs hepatic mitochondrial function by controlling heme homeostasis, thereby contributing to insulin resistance-mediated hepatic mitochondrial dysfunction [62,63]. Heme oxygenase-1 (HO-1) is one of the target genes regulated by FoxO1 [62]. HO-1 gain-of-function increases ferrous iron levels and promotes inflammation in livers [64]; these results indicate that the FoxO1 → HO-1 signaling pathway plays a key role in ferrous iron overload and chronic inflammation under insulin-resistant conditions. Activation of FoxO1 increases TGF-β1 levels, impairing glucose and energy metabolism as well as exacerbating CCL4-induced liver fibrosis [65,66]. In male mice, heart insulin resistance caused by cardiac IRS1 and IRS2 ablation induces heart failure and gradually leads to death, which is rescued by cardiac FoxO1 deletion [20,67]. Cardiac FoxO1 deficiency also improves heart function in both db/db and high-fat diet-induced obese male mice [67]. Additionally, we found that FoxO1 modulates blood pressure by regulating expression levels of the angiotensinogen gene in mice [68]. In addition, we have provided evidence that FoxO1 mediates the beneficial effect of estrogen on glucose dysregulation and heart failure under insulin resistance [69,70]; these results indicate that FoxO1 signaling contributes to the sex dimorphism observed in heart diseases and diabetes. Endothelial dysfunction is highly associated with several diabetes-related vascular complications [71,72]. In diabetic conditions, hyperglycemia, excessive free fatty acids, and insulin resistance induce endothelial dysfunction through increased inflammation and reactive oxygen species (ROS) as well as decreased NO bioavailability, thereby leading to cardiovascular diseases [71]. FoxO1 gain-of-function induces lipid peroxidation and eNOS dysfunction in vascular endothelial cells, and FoxO1 loss-of-function blocks hyperglycemia-induced dysfunction of endothelial cells [73]. These results indicate that FoxO1 is a key mediator that links hyperglycemia to endothelial dysfunction. In summary, FoxO1 plays a pivotal role in insulin resistance-induced hyperglycemia, chronic inflammation, hepatic mitochondrial dysfunction, liver fibrosis, heart failure, and hypertension. Thus, targeting FoxO1 is a promising strategy for the treatment of insulin resistance-associated metabolic diseases. Metformin is a well-established drug for the treatment of T2DM [74]. Epigallocatechin gallate (EGCG), the most abundant catechin in green tea, protects against the development of T2DM [75]. Indeed, our studies have shown that metformin and EGCG inhibit FoxO1-S273 phosphorylation, thus suppressing FoxO1 activity and improving glucose homeostasis [76,77] (Figure 1).

## FoxO1 signaling, metabolic pathways, and diseases



**Figure 1.** FoxO1 plays a pivotal role as a metabolic regulator in hormonal regulation, metformin function, and the influence of bioactive functional foods in both health and disease. Insulin and estrogen stimulate FoxO1 phosphorylation at T24, S253, and S316 through PI3K → AKT signaling, thereby inhibiting FoxO1 activity. Glucagon stimulates FoxO1 phosphorylation at S273 through cAMP → PKA and cAMP → EPAC2 → p38 signaling, thereby increasing FoxO1 activity. Activation of FoxO1 promotes hepatic glucose production, increases hepatokine secretion, impairs cardiac and hepatic mitochondrial function, and induces inflammation during metabolic stress and aging. AC, adenylyl cyclase; AKT, protein kinase B; cAMP, cyclic adenosine monophosphate; EPAC2, exchange protein directly activated by cAMP 2; ER $\alpha$ , estrogen receptor  $\alpha$ ; FoxO1, forkhead/winged helix transcription factor O-class member 1; Gcgr, glucagon receptor; G6Pase, glucose-6-phosphatase; IRS, insulin receptor substrate; P, phosphorylation; PDK, phosphoinositide-dependent protein kinase; PKA, protein kinase A; PI3K, phosphatidylinositol 3-kinase. →: Activation; □: Inhibition [50,51,61–70,73,76,77].

### 3. Dietary Carbohydrates and Glucose Homeostasis

Dietary carbohydrates encompass monosaccharides including glucose, fructose, and galactose; disaccharides including sucrose, lactose, and maltose; oligosaccharides typically consisting of 3–9 molecules in chain length; polysaccharides, notably starch; and dietary fiber. The sugars normally contain mono- and disaccharides. Dietary sugars and starches mainly contribute to energy intake [78]. Carbohydrate intake stimulates insulin secretion, which increases fat storage and decreases lipolysis and fatty acid oxidation. A low-carbohydrate diet improves metabolic syndrome, including lipid and glucose homeostasis [79].

#### 3.1. Dietary Sugars and Insulin Resistance

The increased consumption of refined and simple carbohydrates promotes the development of insulin resistance and T2DM. The World Health Organization and the Food and Agriculture Organization recommended a restriction on free sugar intake to prevent T2DM and obesity [80]. The clinical studies show that high fructose intake (>250 g/day) decreases insulin sensitivity and increases adiposity in both healthy and obese individuals [81,82]. However, moderate fructose intake (<100 g/day) has a limited effect on insulin sensitivity and metabolic health [83]. The overconsumption of dietary sugars promotes the development of insulin resistance, both directly and indirectly. Dietary sugar overconsumption promotes a positive energy balance, thereby increasing body weight and fat



deposition and indirectly leading to insulin resistance and glucose dysregulation. Additionally, fructose reduces hypothalamic malonyl-CoA levels and increases the hunger hormone ghrelin [84–86], thereby stimulating appetite, increasing body weight, and impairing insulin sensitivity. On the other hand, fructose, the sweetest of all naturally occurring carbohydrates, directly causes insulin resistance via increasing hepatic lipid accumulation and promoting inflammation. Fructose is a highly lipogenic sugar and is mainly metabolized in the liver, with very little entering the systemic circulation [87]. Fructose is transported into the liver by GLUT2, phosphorylated into fructose-1-phosphate, and further metabolized to dihydroxyacetone phosphate and glyceraldehyde 3-phosphate, which stimulates *de novo* lipogenesis [88]. Administration of fructose to mice significantly increases the activity of carbohydrate-responsive element-binding protein (ChREBP) and sterol regulatory element-binding protein 1 (SREBP-1c), two important transcription factors stimulating lipogenesis [89,90]. Additionally, fructose intake has been shown to block hepatic fatty acid oxidation, potentially via uric acid-induced mitochondrial oxidative stress [91,92]. Increased hepatic lipid accumulation induces hepatic insulin resistance through PKC-mediated phosphorylation of the insulin receptor at Thr 1160, thereby impairing glucose homeostasis and promoting the development of T2DM [93]. The human studies from Havel's group showed that fructose- but not glucose-sweetened beverage consumption led to a significant increase in lipogenesis, dyslipidemia, and circulating uric acid levels, and a significant decrease in fatty acid oxidation and insulin sensitivity [81]. These different effects between fructose and glucose may be attributed to the marked distinctions in their hepatic metabolism, such as their entry into the glycolytic pathway and the fate of their intermediate metabolites [88].

On the other hand, dietary sugar or fructose impairs immune homeostasis and promotes inflammation, thereby leading to insulin resistance. Dietary fructose is transported into the enterocyte through a specific fructose transporter, GLUT5. Healthy individuals can absorb up to 25 g of fructose [94]. High-fructose diet-induced fructose overload leads to intestinal barrier deterioration and alters gut microbiota composition, thereby increasing endotoxin release, promoting systemic inflammation, and leading to insulin resistance [95,96]. The impairment of the intestinal tissue repair and the gut microbiota environment by fructose leads to intestinal barrier deterioration [97]. Fructose-stimulated endotoxin release increases TNF production in liver macrophages, mediating fructose-induced hepatic insulin resistance and lipogenesis [97,98]. Dietary sugar regulates the crosstalk between the microbiota and intestinal immunity to control insulin resistance and other metabolic disorders. Dietary sugar is a key to disrupting intestinal immune homeostasis via eliminating Th17-inducing microbiota (especially segmented filamentous bacteria). Dietary sugar increases a member of Erysipelotrichaceae to eliminate Th17-inducing microbiota, decreasing Th17 cells, increasing intestinal lipid absorption, and promoting insulin resistance [99]. Of note, a rodent study showed that high fructose intake (30% *w/v*) leads to a more pronounced glucose intolerance in males than in females [100]. In humans, sex differences in the effect of fructose on uric acid concentration but not glucose homeostasis are observed [101]. However, a larger sample size is warranted to investigate the sex difference in fructose-impaired glucose homeostasis in humans.

Low-calorie sweeteners (LCS), including aspartame, saccharin, sucralose, and steviol glycoside, provide an alternative to added sugars and have been used to control body weight gain [102]. The effects of LCS on reduction of caloric intake and body weight gain make LCS a promising approach to controlling blood glucose in patients with T2DM. However, the beneficial effects of LCS are controversial in human studies. In some randomized controlled trials (RCTs), LCSs significantly decreased body weight, body mass index, fat mass, and waist circumference [103]. Contrarily, results from some RCTs fail to show a significant effect of LCSs on weight management [104]. Several observational studies provide evidence that consumption of LCSs is associated with a significantly increased risk of T2DM and a higher incidence of abdominal obesity [105–107]. Further studies are warranted to confirm the effects of LCSs on metabolic diseases.

### 3.2. Dietary Fibers and Insulin Resistance

Dietary fiber is composed of highly complicated substances that include any indigestible carbohydrate and lignin that cannot be degraded in the upper gastrointestinal tract. The viscous, gel-forming, and soluble dietary fiber derived from fruit and certain vegetables suppresses the absorption of macronutrients, reduces postprandial glucose response, and improves lipid profiles. A meta-analysis with 176,117 subjects showed that higher insoluble cereal fiber intake was significantly associated with a lower incidence of diabetes, whereas fruit and vegetable fiber intake had no significant association with the risk of T2DM [108]. Consistently, the consumption of insoluble dietary fiber significantly increases insulin sensitivity in both healthy and diabetic individuals [109–111]. However, other studies provide evidence that soluble dietary fibers decrease postprandial blood glucose and increase insulin sensitivity in both nondiabetic and diabetic subjects [112,113]. Compared to soluble dietary fiber, insoluble dietary fiber has a better effect on attenuation of high-fat diet-induced obesity, body fat composition, and insulin resistance in mice [114]. Short-chain fatty acids (SCFAs), including butyrate, propionate, and acetate, are generated by the gut microbiota through fermenting non-digestible dietary fibers and play an important role in the beneficial effects of dietary fibers on insulin resistance and glucose homeostasis. SCFAs stimulate the secretion of the gut hormone anorexigenic peptide YY (PYY) through free fatty acid receptor 2 (FFAR2), thereby increasing satiety, decreasing body weight, and improving insulin sensitivity [115]. Additionally, SCFAs acetate and propionate increase the secretion of GLP-1 via FFAR2 and 3, contributing to the improvement in glucose tolerance and hepatic insulin sensitivity [116,117]. Wu et al. group reported that glucose infusion in the distal small intestine largely increased plasma GLP-1, with a minimal increase after proximal small intestine glucose infusion [118]. These results suggest that the distal small intestine plays a key role in regulating GLP-1 secretion and modulating glucose homeostasis. Dietary fiber reduces the rate of carbohydrate absorption and increases the interaction between the distal gut and carbohydrate, thereby promoting GLP-1 secretion and improving insulin sensitivity [119,120]. Previous studies have shown that pro-inflammatory markers are reduced by high dietary fiber consumption in both human and rodent models. A randomized trial with 120 obese women showed that consumption of a high-dietary-fiber diet decreased serum proinflammatory marker levels, including IL-6, IL-18, and C-reactive protein (CRP) [121]. In the obese rat model, plasma TNF levels were significantly reduced by the supplementation of dietary fibers for 25 weeks [122]. The anti-inflammatory effect of dietary fiber is potentially attributed to the product of fiber fermentation, butyrate. Previous studies indicate that butyrate attenuates pro-inflammation by inhibiting NF- $\kappa$ B signaling, decreasing IL-12, and increasing IL-10 production in human immune cells [123,124]. Thus, dietary fiber attenuates pro-inflammatory activity through SCFA butyrate, thereby increasing insulin sensitivity and improving glucose tolerance. Intestinal gluconeogenesis-derived glucose is sensed by the gastrointestinal nervous system around the portal vein, transducing signals to the brain regions and regulating energy homeostasis [125,126]. SCFAs, including butyrate and propionate, contribute to intestinal gluconeogenesis and transmit signals to brain regions, thereby executing beneficial effects on insulin sensitivity and glucose metabolism [127].

## 4. Lipid Metabolism and Glucose Homeostasis

### 4.1. Dietary Fat and Insulin Resistance

Dietary fat is highly associated with the incidence of insulin resistance in both mice and humans. In mice, high-fat diet (60% calories derive from fat) feeding for 13 weeks leads to insulin resistance and glucose intolerance [76]. In humans, a higher total fat intake is significantly associated with increased fasting insulin levels, HbA1c, and 2-h post-load glucose levels [128–130]. It is estimated that an increase in dietary fat intake of 40 g/d is correlated with a 3.4-fold increased risk of T2DM [131]. However, several population studies failed to show a significant correlation between total fat intake and the incidence of T2DM, which may be attributed to the quantity and quality of dietary fat. There are

mainly two kinds of dietary fats: saturated and unsaturated fats, which play different roles in the development of insulin resistance. Most epidemiologic and clinical studies consistently show that saturated fat intake is tightly associated with the pathogenesis of insulin resistance and T2DM, whereas polyunsaturated fat intake is significantly associated with improved insulin sensitivity and glucose tolerance [129,130,132–134]. Of note, the beneficial effect of a monounsaturated fatty acid diet is attenuated when total fat intake is over 38% [135]. Additionally, fatty acids with different lengths of carbon chains have distinct effects on insulin sensitivity. Long-chain fatty acids (LCFAs, >C16) are the major fatty acids in the western diet and are highly associated with insulin resistance and impaired glucose homeostasis [136,137]. Medium-chain fatty acids (MCFAs, C8–C12) lead to a decrease in adiposity and an improvement in insulin action compared to LCFAs with equal calories, which is potentially attributed to increased energy expenditure and fatty acid oxidation by MCFAs [138–140]. Short-chain fatty acids (SCFAs, C2–C6) are produced from the fermentation of indigestible food by the gut microbiome. SCFAs exert a beneficial effect on insulin sensitivity by targeting adipose tissue, skeletal muscle, and liver [141,142]. Thus, the quality and quantity of dietary fat intake are pivotal in the development of insulin resistance and T2DM.

#### 4.2. Molecular Mechanisms of FFA-Induced Insulin Resistance

Lipid overload induces insulin resistance in skeletal muscle and liver, thereby leading to defects in insulin-mediated glucose uptake and suppression of HGP, respectively. The detrimental effect of lipid overload on insulin sensitivity is mainly attributed to the increased circulating free fatty acid (FFA) levels, especially saturated free fatty acids (SFAs) [143]. In the KANWU study, high SFA diet intervention significantly impairs insulin sensitivity in both healthy men and women [144]. Aberrant SFA levels stimulate the inflammatory pathway, increase ROS production, generate insulin resistance-associated lipid production, and impair protein folding homeostasis, thereby leading to insulin resistance. Several previous studies showed that SFA treatment activated pro-inflammatory signaling in adipocytes, hepatocytes, and macrophages [145–147], suggesting that SFA is a pro-inflammatory lipid compound. The pro-inflammatory role of SFAs is partially mediated by activation of TLR2/4 signaling [146,148–151]. It is proposed that SFAs activate TLR2/4 signaling indirectly through binding to TLR coreceptors (such as CD36), promoting dimerization of TLR4, and inducing redistribution of c-Src in lipid rafts [152–155]. Activation of SFA → TLR signaling increases inflammatory cytokines such as TNF and activates JNK, thereby inhibiting phosphorylation of IRS1 and attenuating insulin sensitivity [156,157]. In addition, SFAs also induce the activation of the NLRP3-APC inflammasome through increasing mitochondrial ROS and impairing autophagy, thereby promoting IL-1 $\beta$  release and leading to insulin resistance [158]. DAGs, the lipid products of SFAs, are significantly linked to lipid-induced insulin resistance [159]. Plasma membrane-bound sn-1,2-DAG causes hepatic insulin resistance through PKC $\epsilon$ -induced phosphorylation of IR at Thr 1160 [93]. In humans, hepatic DAG content and PKC $\epsilon$  activity are the strongest indicators for hepatic insulin resistance in liver biopsies [160]. SFAs are also involved in ceramide biosynthesis. Increased cellular ceramide levels induce the dephosphorylation of AKT via protein phosphatase 2A, thereby negatively regulating insulin action [161]. Although previous studies showed that inhibition of ceramide synthesis reverses diet-induced insulin resistance in mice [162], there is no significant association between ceramide and hepatic insulin resistance in humans [160]. Thus, DAGs are a major lipid product of SFAs and induce insulin resistance. Unfolded protein response (UPR) or endoplasmic reticulum (ER) stress is activated in the livers of obese mice [163]. Activation of UPR using chemical inducers impairs insulin sensitivity, and attenuation of ER stress by chemical chaperones improves insulin sensitivity [163,164]. UPR-stimulated inositol requiring enzyme-1 (IRE1) activates JNK1, thus leading to phosphorylation of IRS1 at serine 307 and impairing insulin signaling [163]. In cells, lipid overload, especially SFAs, stimulates UPR signaling [165–167]. Therefore, SFAs also impair insulin sensitivity through the activation of UPR signaling



pathways. Circulating fatty acids are sensed by the hypothalamus to maintain glucose homeostasis in a healthy condition [168]. Overnutrition or high-fat diet-induced obesity leads to brain insulin resistance and impairs systemic insulin sensitivity and glucose homeostasis in both humans and mice [169,170]. In the rodent model, brain insulin resistance occurred even after one day of high-fat diet feeding, contributing to subsequent hepatic insulin resistance [170]. Saturated fats, especially palmitic acid, impair hypothalamic insulin signaling by promoting cell membrane localization of PKC- $\theta$  [171]. Saturated fats also induce inflammation and ER stress in the hypothalamus, thereby leading to brain insulin resistance [172–175].

Long-chain polyunsaturated fatty acids (PUFAs), particularly the *n*-3 family, play a key role in regulating insulin sensitivity [176]. Several human studies have shown that omega-3 PUFAs improve insulin sensitivity in both obese non-diabetic and diabetic individuals [177,178]. Omega-3 PUFAs improve insulin sensitivity, potentially through anti-inflammation and PPAR activation. Previous studies showed that omega-3 PUFAs significantly attenuated TNF or TLR2/4 agonist-induced inflammation through GPR120 in macrophages [179,180]. Omega-3 PUFAs promote the association of GPR120 and  $\beta$  arrestin-2 and then induce the internalization of the GPR120/ $\beta$  arrestin-2 complex. The cytoplasmic  $\beta$  arrestin-2 interacts with TAB1 and blocks the interaction between TAB1 and TAK1, thereby inhibiting TAK1 activity, downstream IKK $\beta$ /NF $\kappa$ B and JNK/AP1 signaling, and improving diet-induced insulin resistance [180]. In addition, the anti-inflammatory role of omega-3 PUFAs is potentially mediated by the small lipid mediators (protectins/resolvins) that are metabolized from omega-3 PUFAs. Studies by Serhan et al. show that protectins/resolvins potentially exert an anti-inflammatory role in inflammatory diseases [181,182]. PUFAs are effective ligands for all PPAR isoforms and coordinately regulate the expression levels of genes responsible for lipid oxidation (upregulation) and lipid synthesis (downregulation), thereby improving lipid profiles and increasing insulin sensitivity [176]. C16:1n7-palmitoleate, a natural component in many foods, can be generated in adipose tissue and acts as a lipokine to increase insulin sensitivity and modulate glucose homeostasis [183]. The beneficial effect of palmitoleate is potentially mediated through GPR120 [143]. In healthy humans, ingestion of monounsaturated fatty acid (MUFA) or PUFA-enriched oil leads to higher levels of plasma GLP-1 than saturated fatty acid-enriched oil ingestion [184]. The intake of olive oil and carbohydrate meal leads to a pronounced increase in plasma GLP-1 levels, compared to the intake of butter and carbohydrate meal [185]. Ingestion of olive oil before a carbohydrate meal significantly slows gastric emptying, increases plasma GLP-1 levels, and attenuates postprandial glucose excursion [186]. An in vitro study showed that MUFAs with more than 14 carbon chain lengths significantly stimulate GLP-1 secretion in fetal rat intestinal cells [187]. Therefore, unsaturated fatty acids, including MUFAs and PUFAs, dramatically increase plasma GLP-1 levels, which may contribute to the beneficial effects of MUFAs and PUFAs on insulin sensitivity. Several cohort studies show that diabetes is more prevalent in young men than women [188,189]. Female mice are protected from high-fat diet-induced obesity and hyperglycemia, which is abolished by bilateral ovariectomy and then restored by estrogen supplementation [190]. These results suggest that estrogen plays a key role in protecting against high dietary fat-induced glucose dysregulation. Additionally, healthy young women exhibit a significantly higher GLP-1 response to intraduodenal glucose infusion than men [191]. Thus, increased GLP-1 release in females may contribute to their protection against the development of diabetes. However, whether the sex difference in the GLP-1 response is mediated by estrogen needs to be further investigated. PUFAs, particularly omega-3, improve cognitive function in both young and old individuals [192,193]. A randomized controlled trial shows that omega-3 supplementation attenuates inflammation in middle-aged and old subjects [194], which may contribute to the improvement in brain function and hypothalamic insulin sensitivity.

## 5. Protein Metabolism and Glucose Homeostasis

### 5.1. Dietary Proteins and Insulin Resistance

Dietary protein intake is important for normal growth and development. It is recommended that dietary protein accounts for 10–35% of the total diet. Numerous human studies have reported that a short-term increase in dietary protein consumption significantly decreases body weight. A high-protein diet increases satiety via the gut hormone PYY, stimulates thermogenesis [195], potentially due to the high ATP-consuming protein synthesis, and reduces subsequent energy intake, thereby leading to great weight loss [196,197]. Additionally, protein feeding induces intestinal gluconeogenesis and promotes portal glucose release, which leads to hypothalamic activation through the nerve system around the portal vein and decreases food intake [198,199]. Accordingly, short-term high dietary protein consumption stimulates insulin secretion and reduces blood glucose levels [200]. Consistently, a protein preload significantly decreases postprandial glycemia and increases plasma insulin levels in patients with type 2 diabetes, which is partially attributed to the elevation of GLP-1 and GIP levels [201,202]. A high-protein diet intervention in individuals with type 2 diabetes for 5 weeks improves glucose homeostasis [203]. However, long-term studies (over six months) in humans show that a high-protein diet is significantly associated with increased fasting glucose levels, enhanced gluconeogenesis, and impaired insulin sensitivity [204,205]. A rodent study showed that, compared to a high-fat diet, consumption of a high-fat and high-protein diet for 24 weeks significantly induces  $\beta$ -cell apoptosis and impairs glucose homeostasis, increasing the incidence of T2DM [206]. However, a clinical trial showed that a 12-month high-protein diet intervention has no significant effect on glucose homeostasis in subjects with type 2 diabetes [203]. Additionally, the source of dietary protein is important for the modulation of glucose homeostasis. Compared to casein, soy protein improves glucose tolerance and insulin sensitivity in rat models under high-sucrose diet feeding [207]. A cohort study showed that higher consumption of animal proteins is associated with an increased incidence of type 2 diabetes, whereas higher consumption of vegetable proteins is associated with a modestly decreased risk of type 2 diabetes [208]. The consumption of lean fish containing abundant fish protein and limited fish oil is inversely correlated with the risk of insulin resistance and T2DM [195], suggesting that fish protein potentially protects against the development of T2DM. Several studies indicate that consumption of fish protein increases insulin sensitivity and glucose tolerance, as well as improves lipid profiles [207,209,210].

### 5.2. Amino Acid and Insulin Resistance

In obese individuals, most serum amino acid levels are significantly increased, suggesting that amino acids may play a role in the regulation of insulin resistance [211]. A previous study showed that a short-term increase in plasma amino acids induces insulin resistance in skeletal muscle, decreases glycogen synthesis, and reduces whole-body glucose disposal [212,213]. Amino acid infusion stimulates phosphorylation of IRS1 at serine 312 and 636/639 via activation of the mTOR/S6 kinase 1 signaling pathway, thereby decreasing the interaction of the p85 subunit of PI3K with IRS1 and leading to insulin resistance in skeletal muscle [213,214]. In vitro studies in hepatocytes and adipocytes also show that amino acid treatment negatively modulates insulin sensitivity [215,216]. In addition, amino acids also modulate HGP to regulate glucose homeostasis. On one hand, amino acids act as substrates to contribute to gluconeogenesis. On the other hand, amino acids stimulate glucagon secretion to induce HGP indirectly [217]. These results indicate that amino acid overload may impair insulin sensitivity and glucose homeostasis by targeting the metabolic organs.

Although an amino acid mixture attenuates insulin sensitivity both in vitro and in vivo, different amino acids have distinct effects on insulin sensitivity. Branched-chain amino acids (BCAAs), including valine, isoleucine, and leucine, are critical nutrient signals in regulating body weight and muscle protein synthesis. In obese patients, plasma BCAA levels are significantly elevated [211]. Previous studies have shown that BCAAs are sig-

nificantly associated with the risk of insulin resistance in humans, and BCAAs exacerbate diet-induced insulin resistance in mice [218–220]. Elevated BCAA levels stimulate the activity of mTOR to hamper insulin signaling via inhibitory phosphorylation of IRS1 or E3 ligase Mul1-mediated AKT2 degradation [211,218]. In addition, abnormal BCAA metabolism during obesity leads to the accumulation of toxic BCAA metabolites, thereby activating stress signaling and promoting insulin resistance [221]. Several studies have shown that muscle mitochondrial oxidative capacity is impaired in diabetic individuals [222]. Thus, dysfunctional mitochondrial BCAA catabolism potentially leads to the accumulation of BCAA metabolites in the plasma of people with diabetes, such as BCAA-derived acylcarnitines (C3 and C5), 3-hydroxyisobutyrate (3-HIB), 2-hydroxybutyric acid (2-HB), and 2-ketobutyric acid (2-KB) [221,223]. Aberrant accumulation of these metabolites causes mitochondrial dysfunction, lipotoxicity, and insulin resistance [223–226]. On the other hand, increased BCAA and its metabolites inhibit the activity of the pyruvate dehydrogenase complex (PDH) in the liver and heart, potentially through increased BCAA-derived acetyl-CoA, leading to a significant decrease in glucose uptake and oxidation [221,227]. Thus, BCAA may regulate glucose homeostasis through modulating the activity of PDH. In contrast to BCAAs, plasma glycine levels are significantly reduced in patients with obesity or diabetes [211,228]. Several studies indicate that a low plasma glycine level is a predictor for insulin resistance and T2DM [229–231]. Glycine treatment decreases hepatic oxidative stress marker levels, potentially via increasing glutathione concentrations, thereby improving insulin sensitivity [232]. Arginine is a precursor for nitric oxide. A previous study showed that long-term arginine administration improved insulin resistance in individuals with T2DM [233], suggesting that arginine has a beneficial effect on glucose homeostasis. Indeed, our unpublished data showed that arginine attenuated glucagon-induced HGP through FoxO1. However, the underlying mechanism by which arginine regulates glucose homeostasis needs to be further investigated. Considering the different effects of amino acids on insulin sensitivity, the composition of amino acids in the body plays an important role in the regulation of insulin resistance. This is supported by the evidence that the beneficial effect of cod protein on insulin resistance is recapitulated by an amino acid mixture identified in cod protein-treated rat plasma [210].

## 6. Precision Nutrition and Nutrigenomics

Precision nutrition is becoming an important aspect of metabolic syndrome management. The purpose of precision nutrition is to design a unique nutritional recommendation for each individual according to the combination of an individual's genetics, metabolome, microbiota, and lifestyle factors, thereby preventing metabolic diseases [234]. Based on the International Society of Nutrigenetics/Nutrigenomics (ISNN), precision nutrition should be considered to develop at the following three levels: (1) conventional nutrition based on a general guideline for different populations categorized by age, gender, and other social determinants; (2) individualized nutrition developed by a deep and refined phenotype, including anthropometry, metabolic analysis, physical activity, and others; (3) phenotype-guided nutrition based on the effect of genetic variants or gene expression and their impact on individual responses to specific nutrients [235]. Nutrigenomics aims to investigate the crosstalk among nutrients, diet, and gene expression [235]. The advances in "Omics" technologies, including genomics, transcriptomics, proteomics, metabolomics, metagenomics, and epigenomics, offer a comprehensive method to analyze how specific nutrients affect gene expression and subsequent metabolic responses. Nutrigenetics has provided a better understanding of nutrient or diet effects on metabolic diseases via the discovery of disease-associated genetic variants [235]. The implementation of these disease-associated genetic variants helps to better understand the heterogeneity in nutrient response among different individuals and provides support to develop more precise dietary recommendations in clinical practice. Several studies have shown that macronutrient intake affects the association of genetic markers with metabolic symptoms. Martinez's group evaluated the interaction between diet and genetics using a genetic risk score (GRS) calculated

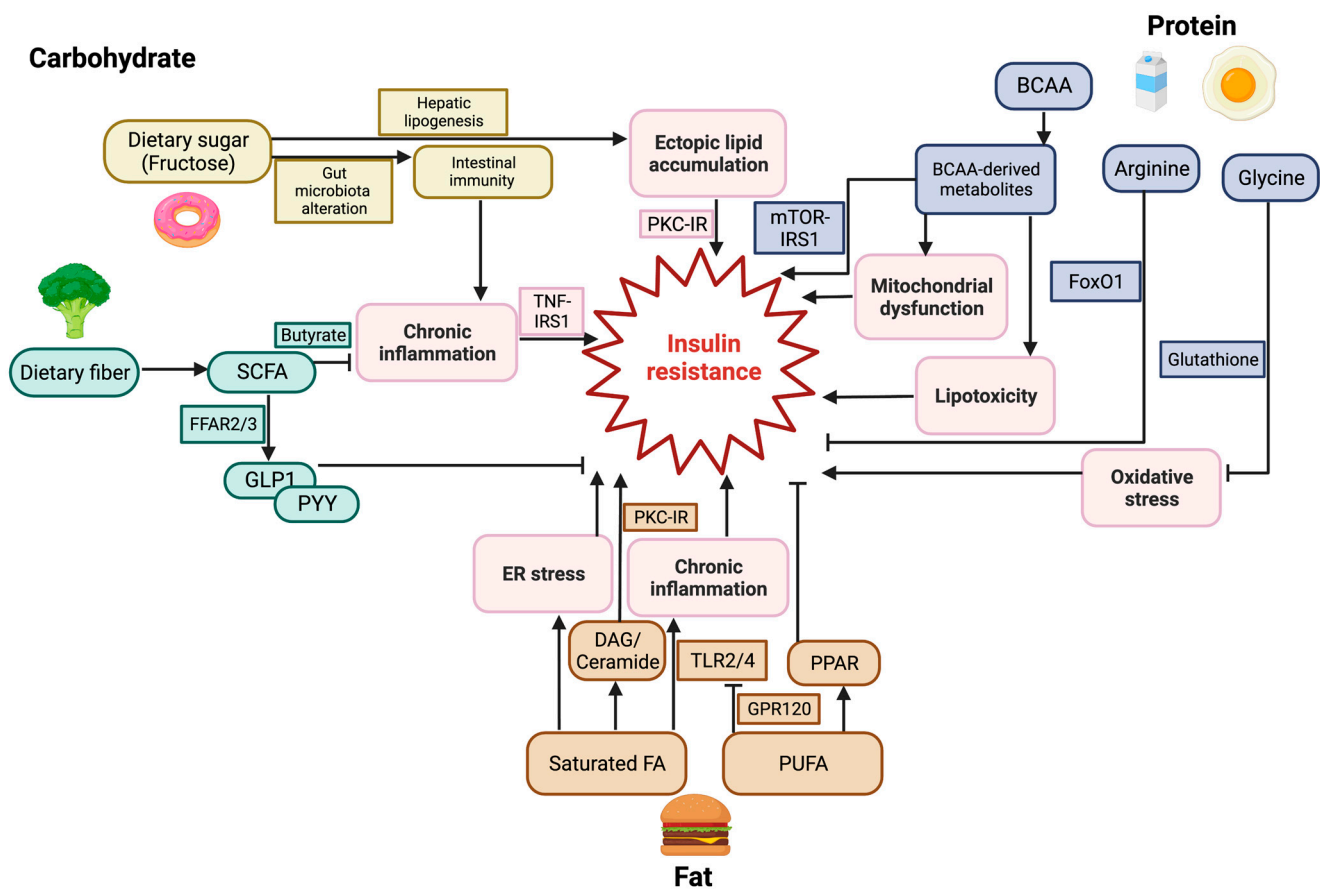
based on 16 metabolic syndrome-associated SNPs. They found that macronutrient intake modified the GRS association with metabolic traits [236]. Other studies also showed that total protein intake and sugar-sweetened beverages modulated the genetic association with obesity [237,238]. Individual genetic information is invaluable for tailoring the most suitable dietary interventions for the prevention or treatment of metabolic diseases. Currently, genetic tests have been used to customize individual diets based on their response to specific nutrients, such as caffeine metabolism-associated SNPs and saturated fat-sensitive APOA2 polymorphism [239,240].

Metabolomics provides a more accurate understanding of the metabolism of nutrients and the impact of nutrients on an individual's health status. Identifying food-derived biomarkers and standardizing the metabolite reference value are important for the application of metabolomics to precision nutrition [234]. Metabolomics is a pillar of deep phenotyping. Metabolic phenotyping based on metabolomics will identify individuals with different responses to interventions, which will help tailor dietary recommendations to the individual [241]. The gut microbiota is affected by antibiotic use and dietary intake, which helps to customize personalized medicine and nutrition. The composition of the microbiota is unique to each individual and represents that individual's metabolic status. A previous study showed that individuals with low bacterial richness are characterized by significant adiposity and insulin resistance [242]. This result suggests that the gut microbiota is a potential target for the treatment of obesity and associated metabolic diseases. The composition and diversity of gut microbiota can be modulated by macronutrient intake, the host genetic makeup, and the interaction between diet and host genetics [243]. Thus, gut microbiota profiling is an important aspect of nutritional intervention. It is promising to perform an integrative analysis of the gut microbiota and metabolomics dataset to evaluate adherence to healthier dietary patterns [244]. Although it is a huge challenge to perform and interpret the integrative multi-omics dataset analysis, there is no doubt that the information we get from multi-omics approaches will improve our understanding of diet-gene-disease interaction and promote the application of precision nutrition in clinical practice.

## 7. Conclusions

T2DM is marked by systemic insulin resistance and  $\beta$ -cell failure-induced insulin deficiency. Overnutrition promotes insulin resistance at multiple levels, including insulin receptor desensitization at the cell surface, inhibition of IRS function through degradation, suppression of PI3K activity, failure to control FoxO1-induced transcriptional changes, and reduced insulin clearance from the bloodstream. Dietary carbohydrate intake induces insulin secretion, and overconsumption of carbohydrates leads to insulin resistance. Fructose is a major driver for the development of insulin resistance through increasing hepatic lipogenesis and impairing gut immunity. Dietary fiber improves insulin sensitivity through gut microbiome-derived SCFAs. Increased dietary fat intake elevates free fatty acid levels, especially unsaturated fatty acids, thereby attenuating insulin sensitivity by inducing pro-inflammatory activity and activating DAG-PKC signaling. PUFA improves insulin resistance through suppression of TLR2/4 signaling and activation of PPAR signaling. The composition of amino acids after dietary protein intake plays a pivotal role in insulin sensitivity and glucose homeostasis. Particularly, increased BCAA levels induce insulin resistance through activation of mTOR-IRS signaling and BCAA metabolite-induced oxidative stress (Figure 2). Short-term protein feeding improves glucose homeostasis, which may be attributed to the increased release of gut hormones, including GLP-1 and GIP. Precision nutrition aims to design a unique nutritional recommendation for each individual according to the combination of an individual's genetics, metabolome, microbiota, and lifestyle factors, thereby preventing metabolic diseases. Understanding the molecular mechanisms of diet-gene interactions will help us apply precision nutrition to clinical practice by integrating multi-omics approaches.





**Figure 2.** Macronutrients regulate insulin resistance and glucose homeostasis through distinct molecular mechanisms. Fructose leads to insulin resistance by increasing hepatic lipogenesis and impairing gut immunity. Dietary fiber improves insulin sensitivity through gut microbiome-derived SCFAs. Increased dietary fat intake elevates free fatty acid levels, especially unsaturated fatty acids, thereby attenuating insulin sensitivity by inducing pro-inflammatory activity and activating DAG-PKC signaling. Increased BCAA levels induce insulin resistance through activation of mTOR-IRS signaling and BCAA metabolite-induced oxidative stress. Glycine improves insulin sensitivity potentially through the generation of glutathione, and arginine contributes to insulin sensitivity by inhibiting FoxO1. BCAA, branched-chain amino acid; DAG, diglyceride; ER stress, endoplasmic reticulum stress; FA, fatty acid; FFAR, free fatty acid receptor; FoxO1, forkhead/winged helix transcription factor O-class member 1; GPR120, G-protein coupled receptor 120; GLP-1, glucagon-like peptide-1; IR, insulin receptor; IRS, insulin receptor substrate; mTOR, mammalian target of rapamycin; PYY, peptide tyrosine tyrosine; PKC, protein kinase C; PPAR, peroxisome proliferator-activated receptor; PUFA, polyunsaturated fatty acid; SCFA, short-chain fatty acid; TLR, toll-like receptor; TNF, tumor necrosis factor. →: Activation; □: Inhibition.

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## References

1. DeFronzo, R.A.; Ferrannini, E.; Groop, L.; Henry, R.R.; Herman, W.H.; Holst, J.J.; Hu, F.B.; Kahn, C.R.; Raz, I.; Shulman, G.I. Type 2 diabetes mellitus. *Nat. Rev. Dis. Primers* **2015**, *1*, 15019. [[CrossRef](#)] [[PubMed](#)]
2. Petersen, M.C.; Shulman, G.I. Mechanisms of insulin action and insulin resistance. *Physiol. Rev.* **2018**, *98*, 2133–2223. [[CrossRef](#)] [[PubMed](#)]
3. Kahn, S. The relative contributions of insulin resistance and beta-cell dysfunction to the pathophysiology of type 2 diabetes. *Diabetologia* **2003**, *46*, 3–19. [[CrossRef](#)] [[PubMed](#)]
4. Czech, M.P. Insulin action and resistance in obesity and type 2 diabetes. *Nat. Med.* **2017**, *23*, 804–814. [[CrossRef](#)]
5. White, M.F.; Kahn, C.R. Insulin action at a molecular level—100 years of progress. *Mol. Metab.* **2021**, *52*, 101304. [[CrossRef](#)] [[PubMed](#)]
6. Guo, S. Insulin signaling, resistance, and the metabolic syndrome: Insights from mouse models to disease mechanisms. *J. Endocrinol.* **2014**, *220*, T1. [[CrossRef](#)]
7. Najjar, S.M.; Perdomo, G. Hepatic insulin clearance: Mechanism and physiology. *Physiology* **2019**, *34*, 198–215. [[CrossRef](#)] [[PubMed](#)]
8. Najjar, S.M.; Caprio, S.; Gastaldelli, A. Insulin Clearance in Health and Disease. *Annu. Rev. Physiol.* **2022**, *85*, 363–381. [[CrossRef](#)] [[PubMed](#)]
9. Wu, T.; Rayner, C.K.; Jones, K.; Horowitz, M. Dietary effects on incretin hormone secretion. *Vitam. Horm.* **2010**, *84*, 81–110.
10. Guo, C.; Huang, T.; Chen, A.; Chen, X.; Wang, L.; Shen, F.; Gu, X. Glucagon-like peptide 1 improves insulin resistance in vitro through anti-inflammation of macrophages. *Braz. J. Med Biol. Res.* **2016**, *49*, e5826. [[CrossRef](#)]
11. Jiang, Y.; Wang, Z.; Ma, B.; Fan, L.; Yi, N.; Lu, B.; Wang, Q.; Liu, R. GLP-1 improves adipocyte insulin sensitivity following induction of endoplasmic reticulum stress. *Front. Pharmacol.* **2018**, *9*, 1168. [[CrossRef](#)]
12. Gao, H.; Wang, X.; Zhang, Z.; Yang, Y.; Yang, J.; Li, X.; Ning, G. GLP-1 amplifies insulin signaling by up-regulation of IR $\beta$ , IRS-1 and GLUT4 in 3T3-L1 adipocytes. *Endocrine* **2007**, *32*, 90–95. [[CrossRef](#)] [[PubMed](#)]
13. MacDonald, P.E.; El-Kholy, W.; Riedel, M.J.; Salapatek, A.M.F.; Light, P.E.; Wheeler, M.B. The multiple actions of GLP-1 on the process of glucose-stimulated insulin secretion. *Diabetes* **2002**, *51* (Suppl. S3), S434–S442. [[CrossRef](#)] [[PubMed](#)]
14. Muscelli, E.; Mari, A.; Casolaro, A.; Camastra, S.; Seghieri, G.; Gastaldelli, A.; Holst, J.J.; Ferrannini, E. Separate impact of obesity and glucose tolerance on the incretin effect in normal subjects and type 2 diabetic patients. *Diabetes* **2008**, *57*, 1340–1348. [[CrossRef](#)] [[PubMed](#)]
15. Ranganath, L.; Beety, J.; Morgan, L.; Wright, J.; Howland, R.; Marks, V. Attenuated GLP-1 secretion in obesity: Cause or consequence? *Gut* **1996**, *38*, 916–919. [[CrossRef](#)]
16. Lynch, C.J.; Adams, S.H. Branched-chain amino acids in metabolic signalling and insulin resistance. *Nat. Rev. Endocrinol.* **2014**, *10*, 723–736. [[CrossRef](#)]
17. Gao, Z.; Hwang, D.; Bataille, F.; Lefevre, M.; York, D.; Quon, M.J.; Ye, J. Serine phosphorylation of insulin receptor substrate 1 by inhibitor  $\kappa$ B kinase complex. *J. Biol. Chem.* **2002**, *277*, 48115–48121. [[CrossRef](#)]
18. Zhang, J.; Gao, Z.; Yin, J.; Quon, M.J.; Ye, J. S6K directly phosphorylates IRS-1 on Ser-270 to promote insulin resistance in response to TNF- $\alpha$  signaling through IKK2. *J. Biol. Chem.* **2008**, *283*, 35375–35382. [[CrossRef](#)]
19. Cai, D.; Yuan, M.; Frantz, D.F.; Melendez, P.A.; Hansen, L.; Lee, J.; Shoelson, S.E. Local and systemic insulin resistance resulting from hepatic activation of IKK- $\beta$  and NF- $\kappa$ B. *Nat. Med.* **2005**, *11*, 183–190. [[CrossRef](#)] [[PubMed](#)]
20. Qi, Y.; Xu, Z.; Zhu, Q.; Thomas, C.; Kumar, R.; Feng, H.; Dostal, D.E.; White, M.F.; Baker, K.M.; Guo, S. Myocardial loss of IRS1 and IRS2 causes heart failure and is controlled by p38 $\alpha$  MAPK during insulin resistance. *Diabetes* **2013**, *62*, 3887–3900. [[CrossRef](#)] [[PubMed](#)]
21. Lee, M.; Kim, M.; Park, J.S.; Lee, S.; You, J.; Ahn, C.W.; Kim, K.R.; Kang, S. Higher glucagon-to-insulin ratio is associated with elevated glycated hemoglobin levels in type 2 diabetes patients. *Korean J. Intern. Med.* **2019**, *34*, 1068. [[CrossRef](#)] [[PubMed](#)]
22. Saltiel, A.R.; Kahn, C.R. Insulin signalling and the regulation of glucose and lipid metabolism. *Nature* **2001**, *414*, 799–806. [[CrossRef](#)] [[PubMed](#)]
23. Boucher, J.; Kleinridders, A.; Kahn, C.R. Insulin receptor signaling in normal and insulin-resistant states. *Cold Spring Harb. Perspect. Biol.* **2014**, *6*, a009191. [[CrossRef](#)]
24. Nagao, H.; Jayavelu, A.K.; Cai, W.; Pan, H.; Dreyfuss, J.M.; Batista, T.M.; Brandão, B.B.; Mann, M.; Kahn, C.R. Unique ligand and kinase-independent roles of the insulin receptor in regulation of cell cycle, senescence and apoptosis. *Nat. Commun.* **2023**, *14*, 57. [[CrossRef](#)]
25. Leney, S.E.; Tavaré, J.M. The molecular basis of insulin-stimulated glucose uptake: Signalling, trafficking and potential drug targets. *J. Endocrinol.* **2009**, *203*, 1–18. [[CrossRef](#)]
26. Sano, H.; Egue, L.; Teruel, M.N.; Fukuda, M.; Chuang, T.D.; Chavez, J.A.; Lienhard, G.E.; McGraw, T.E. Rab10, a target of the AS160 Rab GAP, is required for insulin-stimulated translocation of GLUT4 to the adipocyte plasma membrane. *Cell Metab.* **2007**, *5*, 293–303. [[CrossRef](#)] [[PubMed](#)]
27. Egue, L.; Lee, A.; Chavez, J.A.; Miinea, C.P.; Kane, S.; Lienhard, G.E.; McGraw, T.E. Full intracellular retention of GLUT4 requires AS160 Rab GTPase activating protein. *Cell Metab.* **2005**, *2*, 263–272. [[CrossRef](#)]

28. Larance, M.; Ramm, G.; Stockli, J.; van Dam, E.M.; Winata, S.; Wasinger, V.; Simpson, F.; Graham, M.; Junutula, J.R.; Guilhaus, M. Characterization of the role of the Rab GTPase-activating protein AS160 in insulin-regulated GLUT4 trafficking. *J. Biol. Chem.* **2005**, *280*, 37803–37813. [[CrossRef](#)]
29. Ikononov, O.C.; Sbrissa, D.; Mlak, K.; Shisheva, A. Requirement for PIKfyve enzymatic activity in acute and long-term insulin cellular effects. *Endocrinology* **2002**, *143*, 4742–4754. [[CrossRef](#)]
30. Ikononov, O.C.; Sbrissa, D.; Dondapati, R.; Shisheva, A. ArPIKfyve–PIKfyve interaction and role in insulin-regulated GLUT4 translocation and glucose transport in 3T3-L1 adipocytes. *Exp. Cell Res.* **2007**, *313*, 2404–2416. [[CrossRef](#)]
31. Berwick, D.C.; Dell, G.C.; Welsh, G.I.; Heesom, K.J.; Hers, I.; Fletcher, L.M.; Cooke, F.T.; Tavare, J.M. Protein kinase B phosphorylation of PIKfyve regulates the trafficking of GLUT4 vesicles. *J. Cell Sci.* **2004**, *117*, 5985–5993. [[CrossRef](#)] [[PubMed](#)]
32. Cross, D.A.; Alessi, D.R.; Cohen, P.; Andjelkovich, M.; Hemmings, B.A. Inhibition of glycogen synthase kinase-3 by insulin mediated by protein kinase B. *Nature* **1995**, *378*, 785–789. [[CrossRef](#)]
33. Dong, X.C.; Copps, K.D.; Guo, S.; Li, Y.; Kollipara, R.; DePinho, R.A.; White, M.F. Inactivation of hepatic Foxo1 by insulin signaling is required for adaptive nutrient homeostasis and endocrine growth regulation. *Cell Metab.* **2008**, *8*, 65–76. [[CrossRef](#)] [[PubMed](#)]
34. Schmoll, D.; Walker, K.S.; Alessi, D.R.; Grempler, R.; Burchell, A.; Guo, S.; Walther, R.; Unterman, T.G. Regulation of glucose-6-phosphatase gene expression by protein kinase B $\alpha$  and the forkhead transcription factor FKHR. Evidence for insulin response unit-dependent and -independent effects of insulin on promoter activity. *J. Biol. Chem.* **2000**, *275*, 36324–36333. [[CrossRef](#)] [[PubMed](#)]
35. Rena, G.; Guo, S.; Cichy, S.C.; Unterman, T.G.; Cohen, P. Phosphorylation of the transcription factor forkhead family member FKHR by protein kinase B. *J. Biol. Chem.* **1999**, *274*, 17179–17183. [[CrossRef](#)] [[PubMed](#)]
36. Guo, S.; Rena, G.; Cichy, S.; He, X.; Cohen, P.; Unterman, T. Phosphorylation of serine 256 by protein kinase B disrupts transactivation by FKHR and mediates effects of insulin on insulin-like growth factor-binding protein-1 promoter activity through a conserved insulin response sequence. *J. Biol. Chem.* **1999**, *274*, 17184–17192. [[CrossRef](#)] [[PubMed](#)]
37. Yoon, N.A.; Diano, S. Hypothalamic glucose-sensing mechanisms. *Diabetologia* **2021**, *64*, 985–993. [[CrossRef](#)] [[PubMed](#)]
38. Könnner, A.C.; Janoschek, R.; Plum, L.; Jordan, S.D.; Rother, E.; Ma, X.; Xu, C.; Enriori, P.; Hampel, B.; Barsh, G.S. Insulin action in AgRP-expressing neurons is required for suppression of hepatic glucose production. *Cell Metab.* **2007**, *5*, 438–449. [[CrossRef](#)]
39. Inoue, H.; Ogawa, W.; Asakawa, A.; Okamoto, Y.; Nishizawa, A.; Matsumoto, M.; Teshigawara, K.; Matsuki, Y.; Watanabe, E.; Hiramatsu, R. Role of hepatic STAT3 in brain-insulin action on hepatic glucose production. *Cell Metab.* **2006**, *3*, 267–275. [[CrossRef](#)]
40. Scherer, T.; O'Hare, J.; Diggs-Andrews, K.; Schweiger, M.; Cheng, B.; Lindtner, C.; Zielinski, E.; Vempati, P.; Su, K.; Dighe, S. Brain insulin controls adipose tissue lipolysis and lipogenesis. *Cell Metab.* **2011**, *13*, 183–194. [[CrossRef](#)]
41. Heni, M.; Wagner, R.; Kullmann, S.; Veit, R.; Mat Husin, H.; Linder, K.; Benkendorff, C.; Peter, A.; Stefan, N.; Häring, H.-U. Central insulin administration improves whole-body insulin sensitivity via hypothalamus and parasympathetic outputs in men. *Diabetes* **2014**, *63*, 4083–4088. [[CrossRef](#)] [[PubMed](#)]
42. Benedict, C.; Brede, S.; Schiöth, H.B.; Lehnert, H.; Schultes, B.; Born, J.; Hallschmid, M. Intranasal insulin enhances postprandial thermogenesis and lowers postprandial serum insulin levels in healthy men. *Diabetes* **2011**, *60*, 114–118. [[CrossRef](#)] [[PubMed](#)]
43. Hallschmid, M.; Benedict, C.; Schultes, B.; Fehm, H.-L.; Born, J.; Kern, W. Intranasal insulin reduces body fat in men but not in women. *Diabetes* **2004**, *53*, 3024–3029. [[CrossRef](#)]
44. Gelling, R.; Du, X.; Dichmann, D.; Rømer, J.; Huang, H.; Cui, L.; Obici, S.; Tang, B.; Holst, J.; Fledelius, C. Lower blood glucose, hyperglucagonemia, and pancreatic  $\alpha$  cell hyperplasia in glucagon receptor knockout mice. *Proc. Natl. Acad. Sci. USA* **2003**, *100*, 1438–1443. [[CrossRef](#)] [[PubMed](#)]
45. Cheng, X.; Ji, Z.; Tsalkova, T.; Mei, F. Epac and PKA: A tale of two intracellular cAMP receptors. *Acta Biochim. Biophys. Sin.* **2008**, *40*, 651–662. [[CrossRef](#)]
46. Rui, L. Energy metabolism in the liver. *Compr. Physiol.* **2014**, *4*, 177. [[PubMed](#)]
47. Oh, K.-J.; Han, H.-S.; Kim, M.-J.; Koo, S.-H. CREB and FoxO1: Two transcription factors for the regulation of hepatic gluconeogenesis. *BMB Rep.* **2013**, *46*, 567. [[CrossRef](#)] [[PubMed](#)]
48. Koo, S.-H.; Flechner, L.; Qi, L.; Zhang, X.; Sreaton, R.A.; Jeffries, S.; Hedrick, S.; Xu, W.; Boussouar, F.; Brindle, P. The CREB coactivator TORC2 is a key regulator of fasting glucose metabolism. *Nature* **2005**, *437*, 1109. [[CrossRef](#)]
49. Xu, W.; Kasper, L.H.; Lerach, S.; Jeevan, T.; Brindle, P.K. Individual CREB-target genes dictate usage of distinct cAMP-responsive coactivation mechanisms. *EMBO J.* **2007**, *26*, 2890–2903. [[CrossRef](#)] [[PubMed](#)]
50. Wu, Y.; Pan, Q.; Yan, H.; Zhang, K.; Guo, X.; Xu, Z.; Yang, W.; Qi, Y.; Guo, C.A.; Hornsby, C. Novel mechanism of Foxo1 phosphorylation in glucagon signaling in control of glucose homeostasis. *Diabetes* **2018**, *67*, 2167–2182. [[CrossRef](#)]
51. Yang, W.; Liao, W.; Li, X.; Ai, W.; Pan, Q.; Shen, Z.; Jiang, W.; Guo, S. Hepatic p38 $\alpha$  MAPK controls gluconeogenesis via FOXO1 phosphorylation at S273 during glucagon signalling in mice. *Diabetologia* **2023**, *66*, 1322–1339. [[CrossRef](#)]
52. Kim, J.; Okamoto, H.; Huang, Z.; Anguiano, G.; Chen, S.; Liu, Q.; Cavino, K.; Xin, Y.; Na, E.; Hamid, R. Amino acid transporter Slc38a5 controls glucagon receptor inhibition-induced pancreatic  $\alpha$  cell hyperplasia in mice. *Cell Metab.* **2017**, *25*, 1348–1361. [[CrossRef](#)]

53. Perry, R.J.; Camporez, J.-P.G.; Kursawe, R.; Titchenell, P.M.; Zhang, D.; Perry, C.J.; Jurczak, M.J.; Abudukadier, A.; Han, M.S.; Zhang, X.-M. Hepatic acetyl CoA links adipose tissue inflammation to hepatic insulin resistance and type 2 diabetes. *Cell* **2015**, *160*, 745–758. [[CrossRef](#)] [[PubMed](#)]
54. Perry, R.J.; Zhang, D.; Guerra, M.T.; Brill, A.L.; Goedeke, L.; Nasiri, A.R.; Rabin-Court, A.; Wang, Y.; Peng, L.; Dufour, S. Glucagon stimulates gluconeogenesis by INSP3R1-mediated hepatic lipolysis. *Nature* **2020**, *579*, 279–283. [[CrossRef](#)] [[PubMed](#)]
55. Mighiu, P.I.; Yue, J.T.; Filippi, B.M.; Abraham, M.A.; Chari, M.; Lam, C.K.; Yang, C.S.; Christian, N.R.; Charron, M.J.; Lam, T.K. Hypothalamic glucagon signaling inhibits hepatic glucose production. *Nat. Med.* **2013**, *19*, 766–772. [[CrossRef](#)]
56. Abraham, M.A.; Yue, J.T.; LaPierre, M.P.; Rutter, G.A.; Light, P.E.; Filippi, B.M.; Lam, T.K. Hypothalamic glucagon signals through the KATP channels to regulate glucose production. *Mol. Metab.* **2014**, *3*, 202–208. [[CrossRef](#)] [[PubMed](#)]
57. Zhang, K.; Li, L.; Qi, Y.; Zhu, X.; Gan, B.; DePinho, R.A.; Averitt, T.; Guo, S. Hepatic suppression of Foxo1 and Foxo3 causes hypoglycemia and hyperlipidemia in mice. *Endocrinology* **2012**, *153*, 631–646. [[CrossRef](#)]
58. Haeusler, R.A.; Kaestner, K.H.; Accili, D. FoxOs function synergistically to promote glucose production. *J. Biol. Chem.* **2010**, *285*, 35245–35248. [[CrossRef](#)]
59. Matsuzaki, H.; Daitoku, H.; Hatta, M.; Tanaka, K.; Fukamizu, A. Insulin-induced phosphorylation of FKHR (Foxo1) targets to proteasomal degradation. *Proc. Natl. Acad. Sci. USA* **2003**, *100*, 11285–11290. [[CrossRef](#)]
60. Zhang, K.; Guo, X.; Yan, H.; Wu, Y.; Pan, Q.; Shen, J.Z.; Li, X.; Chen, Y.; Li, L.; Qi, Y. Phosphorylation of forkhead protein FoxO1 at S253 regulates glucose homeostasis in mice. *Endocrinology* **2019**, *160*, 1333–1347. [[CrossRef](#)]
61. Yang, W.; Kim, D.M.; Jiang, W.; Ai, W.; Pan, Q.; Rahman, S.; Cai, J.J.; Brashear, W.A.; Sun, Y.; Guo, S. Suppression of FOXO1 attenuates inflamm-aging and improves liver function during aging. *Aging Cell* **2023**, *22*, e13968. [[CrossRef](#)]
62. Cheng, Z.; Guo, S.; Copps, K.; Dong, X.; Kollipara, R.; Rodgers, J.T.; Depinho, R.A.; Puigserver, P.; White, M.F. Foxo1 integrates insulin signaling with mitochondrial function in the liver. *Nat. Med.* **2009**, *15*, 1307–1311. [[CrossRef](#)] [[PubMed](#)]
63. Yang, W.; Yan, H.; Pan, Q.; Shen, J.Z.; Zhou, F.; Wu, C.; Sun, Y.; Guo, S. Glucagon regulates hepatic mitochondrial function and biogenesis through FOXO1. *J. Endocrinol.* **2019**, *241*, 265–278. [[CrossRef](#)] [[PubMed](#)]
64. Liao, W.; Yang, W.; Shen, Z.; Ai, W.; Pan, Q.; Sun, Y.; Guo, S. Heme Oxygenase-1 Regulates Ferrous Iron and Foxo1 in Control of Hepatic Gluconeogenesis. *Diabetes* **2021**, *70*, 696–709. [[CrossRef](#)] [[PubMed](#)]
65. Pan, Q.; Ai, W.; Chen, Y.; Kim, D.M.; Shen, Z.; Yang, W.; Jiang, W.; Sun, Y.; Safe, S.; Guo, S. Reciprocal regulation of hepatic TGF- $\beta$ 1 and Foxo1 controls gluconeogenesis and energy expenditure. *Diabetes* **2023**, *72*, 1193–1206. [[CrossRef](#)]
66. Pan, Q.; Gao, M.; Kim, D.; Ai, W.; Yang, W.; Jiang, W.; Brashear, W.; Dai, Y.; Li, S.; Sun, Y. Hepatocyte FoxO1 deficiency protects from liver fibrosis via reducing inflammation and TGF- $\beta$ 1 mediated HSC activation. *Cell. Mol. Gastroenterol. Hepatol.* **2023**. [[CrossRef](#)] [[PubMed](#)]
67. Qi, Y.; Zhu, Q.; Zhang, K.; Thomas, C.; Wu, Y.; Kumar, R.; Baker, K.M.; Xu, Z.; Chen, S.; Guo, S. Activation of Foxo1 by insulin resistance promotes cardiac dysfunction and  $\beta$ -myosin heavy chain gene expression. *Circ. Heart Fail.* **2015**, *8*, 198–208. [[CrossRef](#)]
68. Qi, Y.; Zhang, K.; Wu, Y.; Xu, Z.; Yong, Q.C.; Kumar, R.; Baker, K.M.; Zhu, Q.; Chen, S.; Guo, S. Novel mechanism of blood pressure regulation by Forkhead box class O1-Mediated transcriptional control of hepatic angiotensinogen. *Hypertension* **2014**, *64*, 1131–1140. [[CrossRef](#)]
69. Yan, H.; Yang, W.; Zhou, F.; Li, X.; Pan, Q.; Shen, Z.; Han, G.; Newell-Fugate, A.; Tian, Y.; Majeti, R. Estrogen improves insulin sensitivity and suppresses gluconeogenesis via the transcription factor Foxo1. *Diabetes* **2019**, *68*, 291–304. [[CrossRef](#)]
70. Yan, H.; Yang, W.; Zhou, F.; Pan, Q.; Allred, K.; Allred, C.; Sun, Y.; Threadgill, D.; Dostal, D.; Tong, C. Estrogen protects cardiac function and energy metabolism in dilated cardiomyopathy induced by loss of cardiac IRS1 and IRS2. *Circ. Heart Fail.* **2022**, *15*, e008758. [[CrossRef](#)]
71. Sena, C.M.; Pereira, A.M.; Seica, R. Endothelial dysfunction—A major mediator of diabetic vascular disease. *Biochim. Biophys. Acta-Mol. Basis Dis.* **2013**, *1832*, 2216–2231. [[CrossRef](#)]
72. Singh, D.K.; Winocour, P.; Farrington, K. Endothelial cell dysfunction, medial arterial calcification and osteoprotegerin in diabetes. *Br. J. Diabetes Vasc. Dis.* **2010**, *10*, 71–77. [[CrossRef](#)]
73. Tanaka, J.; Qiang, L.; Banks, A.S.; Welch, C.L.; Matsumoto, M.; Kitamura, T.; Ido-Kitamura, Y.; DePinho, R.A.; Accili, D. Foxo1 links hyperglycemia to LDL oxidation and endothelial nitric oxide synthase dysfunction in vascular endothelial cells. *Diabetes* **2009**, *58*, 2344–2354. [[CrossRef](#)]
74. Rena, G.; Hardie, D.G.; Pearson, E.R. The mechanisms of action of metformin. *Diabetologia* **2017**, *60*, 1577–1585. [[CrossRef](#)]
75. Wolfram, S. Effects of green tea and EGCG on cardiovascular and metabolic health. *J. Am. Coll. Nutr.* **2007**, *26*, 373S–388S. [[CrossRef](#)]
76. Guo, X.; Li, X.; Yang, W.; Liao, W.; Shen, J.Z.; Ai, W.; Pan, Q.; Sun, Y.; Zhang, K.; Zhang, R.; et al. Metformin Targets Foxo1 to Control Glucose Homeostasis. *Biomolecules* **2021**, *11*, 873. [[CrossRef](#)]
77. Li, X.; Chen, Y.; Shen, J.Z.; Pan, Q.; Yang, W.; Yan, H.; Liu, H.; Ai, W.; Liao, W.; Guo, S. Epigallocatechin gallate inhibits hepatic glucose production in primary hepatocytes via downregulating PKA signaling pathways and transcriptional factor FoxO1. *J. Agric. Food Chem.* **2019**, *67*, 3651–3661. [[CrossRef](#)] [[PubMed](#)]
78. MacDonald, I.A. A review of recent evidence relating to sugars, insulin resistance and diabetes. *Eur. J. Nutr.* **2016**, *55*, 17–23. [[CrossRef](#)] [[PubMed](#)]



79. Hyde, P.N.; Sapper, T.N.; Crabtree, C.D.; LaFountain, R.A.; Bowling, M.L.; Buga, A.; Fell, B.; McSwiney, F.T.; Dickerson, R.M.; Miller, V.J. Dietary carbohydrate restriction improves metabolic syndrome independent of weight loss. *JCI Insight* **2019**, *4*, e128308. [[CrossRef](#)]
80. Laville, M.; Nazare, J.A. Diabetes, insulin resistance and sugars. *Obes. Rev.* **2009**, *10*, 24–33. [[CrossRef](#)]
81. Stanhope, K.L.; Schwarz, J.M.; Keim, N.L.; Griffen, S.C.; Bremer, A.A.; Graham, J.L.; Hatcher, B.; Cox, C.L.; Dyachenko, A.; Zhang, W. Consuming fructose-sweetened, not glucose-sweetened, beverages increases visceral adiposity and lipids and decreases insulin sensitivity in overweight/obese humans. *J. Clin. Invest.* **2009**, *119*, 1322–1334. [[CrossRef](#)]
82. Lecoultre, V.; Egli, L.; Carrel, G.; Theytaz, F.; Kreis, R.; Schneiter, P.; Boss, A.; Zwygart, K.; Lê, K.A.; Bortolotti, M. Effects of fructose and glucose overfeeding on hepatic insulin sensitivity and intrahepatic lipids in healthy humans. *Obesity* **2013**, *21*, 782–785. [[CrossRef](#)] [[PubMed](#)]
83. Heden, T.D.; Liu, Y.; Park, Y.-M.; Nyhoff, L.M.; Winn, N.C.; Kanaley, J.A. Moderate amounts of fructose-or glucose-sweetened beverages do not differentially alter metabolic health in male and female adolescents. *Am. J. Clin. Nutr.* **2014**, *100*, 796–805. [[CrossRef](#)]
84. Cha, S.H.; Wolfgang, M.; Tokutake, Y.; Chohnan, S.; Lane, M.D. Differential effects of central fructose and glucose on hypothalamic malonyl-CoA and food intake. *Proc. Natl. Acad. Sci. USA* **2008**, *105*, 16871–16875. [[CrossRef](#)] [[PubMed](#)]
85. Teff, K.L.; Elliott, S.S.; Tschöp, M.; Kieffer, T.J.; Rader, D.; Heiman, M.; Townsend, R.R.; Keim, N.L.; D’Alessio, D.; Havel, P.J. Dietary fructose reduces circulating insulin and leptin, attenuates postprandial suppression of ghrelin, and increases triglycerides in women. *J. Clin. Endocrinol. Metab.* **2004**, *89*, 2963–2972. [[CrossRef](#)]
86. Miller, C.C.; Martin, R.J.; Whitney, M.L.; Edwards, G.L. Intracerebroventricular injection of fructose stimulates feeding in rats. *Nutr. Neurosci.* **2002**, *5*, 359–362. [[CrossRef](#)] [[PubMed](#)]
87. Stanhope, K.L. Sugar consumption, metabolic disease and obesity: The state of the controversy. *Crit. Rev. Clin. Lab. Sci.* **2016**, *53*, 52–67. [[CrossRef](#)]
88. Tappy, L.; Lê, K.-A. Metabolic effects of fructose and the worldwide increase in obesity. *Physiol. Rev.* **2010**, *90*, 23–46. [[CrossRef](#)]
89. Zhang, C.; Chen, X.; Zhu, R.-M.; Zhang, Y.; Yu, T.; Wang, H.; Zhao, H.; Zhao, M.; Ji, Y.-L.; Chen, Y.-H. Endoplasmic reticulum stress is involved in hepatic SREBP-1c activation and lipid accumulation in fructose-fed mice. *Toxicol. Lett.* **2012**, *212*, 229–240. [[CrossRef](#)]
90. Kim, M.-S.; Krawczyk, S.A.; Doridot, L.; Fowler, A.J.; Wang, J.X.; Trauger, S.A.; Noh, H.-L.; Kang, H.J.; Meissen, J.K.; Blatnik, M. ChREBP regulates fructose-induced glucose production independently of insulin signaling. *J. Clin. Invest.* **2019**, *126*, 4372–4386. [[CrossRef](#)]
91. Jensen, T.; Abdelmalek, M.F.; Sullivan, S.; Nadeau, K.J.; Green, M.; Roncal, C.; Nakagawa, T.; Kuwabara, M.; Sato, Y.; Kang, D.-H. Fructose and sugar: A major mediator of non-alcoholic fatty liver disease. *J. Hepatol.* **2018**, *68*, 1063–1075. [[CrossRef](#)] [[PubMed](#)]
92. Lanaspá, M.A.; Sanchez-Lozada, L.G.; Choi, Y.-J.; Cicerchi, C.; Kanbay, M.; Roncal-Jimenez, C.A.; Ishimoto, T.; Li, N.; Marek, G.; Duranay, M. Uric acid induces hepatic steatosis by generation of mitochondrial oxidative stress: Potential role in fructose-dependent and-independent fatty liver. *J. Biol. Chem.* **2012**, *287*, 40732–40744. [[CrossRef](#)]
93. Lyu, K.; Zhang, Y.; Zhang, D.; Kahn, M.; Ter Horst, K.W.; Rodrigues, M.R.; Gaspar, R.C.; Hirabara, S.M.; Luukkonen, P.K.; Lee, S. A membrane-bound diacylglycerol species induces PKC $\epsilon$ -mediated hepatic insulin resistance. *Cell Metab.* **2020**, *32*, 654–664.e655. [[CrossRef](#)] [[PubMed](#)]
94. Rao, S.S.; Attaluri, A.; Anderson, L.; Stumbo, P. Ability of the normal human small intestine to absorb fructose: Evaluation by breath testing. *Clin. Gastroenterol. Hepatol.* **2007**, *5*, 959–963. [[CrossRef](#)]
95. Wang, Y.; Qi, W.; Song, G.; Pang, S.; Peng, Z.; Li, Y.; Wang, P. High-fructose diet increases inflammatory cytokines and alters gut microbiota composition in rats. *Mediat. Inflamm.* **2020**, *2020*, 6672636. [[CrossRef](#)] [[PubMed](#)]
96. Do, M.H.; Lee, E.; Oh, M.-J.; Kim, Y.; Park, H.-Y. High-glucose or-fructose diet cause changes of the gut microbiota and metabolic disorders in mice without body weight change. *Nutrients* **2018**, *10*, 761. [[CrossRef](#)]
97. Todoric, J.; Di Caro, G.; Reibe, S.; Henstridge, D.C.; Green, C.R.; Vrbanc, A.; Ceteci, F.; Conche, C.; McNulty, R.; Shalpour, S. Fructose stimulated de novo lipogenesis is promoted by inflammation. *Nat. Metab.* **2020**, *2*, 1034–1045. [[CrossRef](#)]
98. Uysal, K.T.; Wiesbrock, S.M.; Marino, M.W.; Hotamisligil, G.S. Protection from obesity-induced insulin resistance in mice lacking TNF- $\alpha$  function. *Nature* **1997**, *389*, 610–614. [[CrossRef](#)]
99. Kawano, Y.; Edwards, M.; Huang, Y.; Bilate, A.M.; Araujo, L.P.; Tanoue, T.; Atarashi, K.; Ladinsky, M.S.; Reiner, S.L.; Wang, H.H. Microbiota imbalance induced by dietary sugar disrupts immune-mediated protection from metabolic syndrome. *Cell* **2022**, *185*, 3501–3519.e3520. [[CrossRef](#)]
100. De Souza, L.; de Medeiros Barros, W.; De Souza, R.M.; Delanogare, E.; Machado, A.E.; Braga, S.P.; Rosa, G.K.; Nardi, G.M.; Rafacho, A.; Speretta, G.F.F. Impact of different fructose concentrations on metabolic and behavioral parameters of male and female mice. *Physiol. Behav.* **2021**, *228*, 113187. [[CrossRef](#)]
101. Teff, K.L.; Grudziak, J.; Townsend, R.R.; Dunn, T.N.; Grant, R.W.; Adams, S.H.; Keim, N.L.; Cummings, B.P.; Stanhope, K.L.; Havel, P.J. Endocrine and metabolic effects of consuming fructose-and glucose-sweetened beverages with meals in obese men and women: Influence of insulin resistance on plasma triglyceride responses. *J. Clin. Endocrinol. Metab.* **2009**, *94*, 1562–1569. [[CrossRef](#)]
102. Johnston, C.A.; Stevens, B.; Foreyt, J.P. The role of low-calorie sweeteners in diabetes. *Eur. Endocrinol.* **2013**, *9*, 96. [[CrossRef](#)]

103. Miller, P.E.; Perez, V. Low-calorie sweeteners and body weight and composition: A meta-analysis of randomized controlled trials and prospective cohort studies. *Am. J. Clin. Nutr.* **2014**, *100*, 765–777. [[CrossRef](#)]
104. Azad, M.B.; Abou-Setta, A.M.; Chauhan, B.F.; Rabbani, R.; Lys, J.; Copstein, L.; Mann, A.; Jeyaraman, M.M.; Reid, A.E.; Fiander, M. Nonnutritive sweeteners and cardiometabolic health: A systematic review and meta-analysis of randomized controlled trials and prospective cohort studies. *Cmaj* **2017**, *189*, E929–E939. [[CrossRef](#)]
105. Fowler, S.P.; Williams, K.; Hazuda, H.P. Diet soda intake is associated with long-term increases in waist circumference in a biethnic cohort of older adults: The San Antonio Longitudinal Study of Aging. *J. Am. Geriatr. Soc.* **2015**, *63*, 708–715. [[CrossRef](#)] [[PubMed](#)]
106. Chia, C.W.; Shardell, M.; Tanaka, T.; Liu, D.D.; Gravenstein, K.S.; Simonsick, E.M.; Egan, J.M.; Ferrucci, L. Chronic low-calorie sweetener use and risk of abdominal obesity among older adults: A cohort study. *PLoS ONE* **2016**, *11*, e0167241. [[CrossRef](#)]
107. Nettleton, J.A.; Lutsey, P.L.; Wang, Y.; Lima, J.A.; Michos, E.D.; Jacobs, D.R., Jr. Diet soda intake and risk of incident metabolic syndrome and type 2 diabetes in the Multi-Ethnic Study of Atherosclerosis (MESA). *Diabetes Care* **2009**, *32*, 688–694. [[CrossRef](#)] [[PubMed](#)]
108. Schulze, M.B.; Schulz, M.; Heidemann, C.; Schienkiewitz, A.; Hoffmann, K.; Boeing, H. Fiber and magnesium intake and incidence of type 2 diabetes: A prospective study and meta-analysis. *Arch. Intern. Med.* **2007**, *167*, 956–965. [[CrossRef](#)]
109. Robertson, M.D.; Bickerton, A.S.; Dennis, A.L.; Vidal, H.; Frayn, K.N. Insulin-sensitizing effects of dietary resistant starch and effects on skeletal muscle and adipose tissue metabolism. *Am. J. Clin. Nutr.* **2005**, *82*, 559–567. [[CrossRef](#)]
110. Weickert, M.O.; Möhlig, M.; Schöfl, C.; Arafat, A.M.; Otto, B.; Viehoff, H.; Koebnick, C.; Kohl, A.; Spranger, J.; Pfeiffer, A.F. Cereal fiber improves whole-body insulin sensitivity in overweight and obese women. *Diabetes Care* **2006**, *29*, 775–780. [[CrossRef](#)] [[PubMed](#)]
111. Pereira, M.A.; Jacobs, D.R., Jr.; Pins, J.J.; Raatz, S.K.; Gross, M.D.; Slavin, J.L.; Seaquist, E.R. Effect of whole grains on insulin sensitivity in overweight hyperinsulinemic adults. *Am. J. Clin. Nutr.* **2002**, *75*, 848–855. [[CrossRef](#)]
112. Hanai, H.; Ikuma, M.; Sato, Y.; Iida, T.; Hosoda, Y.; Matsushita, I.; Nogaki, A.; Yamada, M.; Kaneko, E. Long-term effects of water-soluble corn bran hemicellulose on glucose tolerance in obese and non-obese patients: Improved insulin sensitivity and glucose metabolism in obese subjects. *Biosci. Biotechnol. Biochem.* **1997**, *61*, 1358–1361. [[CrossRef](#)]
113. Sierra, M.; Garcia, J.; Fernández, N.; Diez, M.; Calle, A.; Sahagun, A. Effects of ispaghula husk and guar gum on postprandial glucose and insulin concentrations in healthy subjects. *Eur. J. Clin. Nutr.* **2001**, *55*, 235–243. [[CrossRef](#)] [[PubMed](#)]
114. Isken, F.; Klaus, S.; Osterhoff, M.; Pfeiffer, A.F.; Weickert, M.O. Effects of long-term soluble vs. insoluble dietary fiber intake on high-fat diet-induced obesity in C57BL/6J mice. *J. Nutr. Biochem.* **2010**, *21*, 278–284. [[CrossRef](#)] [[PubMed](#)]
115. Brooks, L.; Viardot, A.; Tsakmaki, A.; Stolarczyk, E.; Howard, J.K.; Cani, P.D.; Everard, A.; Sleeth, M.L.; Psychas, A.; Anastasovskaj, J. Fermentable carbohydrate stimulates FFAR2-dependent colonic PYY cell expansion to increase satiety. *Mol. Metab.* **2017**, *6*, 48–60. [[CrossRef](#)] [[PubMed](#)]
116. Cani, P.D.; Knauf, C.; Iglesias, M.A.; Drucker, D.J.; Delzenne, N.M.; Burcelin, R. Improvement of glucose tolerance and hepatic insulin sensitivity by oligofructose requires a functional glucagon-like peptide 1 receptor. *Diabetes* **2006**, *55*, 1484–1490. [[CrossRef](#)]
117. Tolhurst, G.; Heffron, H.; Lam, Y.S.; Parker, H.E.; Habib, A.M.; Diakogiannaki, E.; Cameron, J.; Grosse, J.; Reimann, F.; Gribble, F.M. Short-chain fatty acids stimulate glucagon-like peptide-1 secretion via the G-protein-coupled receptor FFAR2. *Diabetes* **2012**, *61*, 364–371. [[CrossRef](#)]
118. Zhang, X.; Young, R.L.; Bound, M.; Hu, S.; Jones, K.L.; Horowitz, M.; Rayner, C.K.; Wu, T. Comparative effects of proximal and distal small intestinal glucose exposure on glycemia, incretin hormone secretion, and the incretin effect in health and type 2 diabetes. *Diabetes Care* **2019**, *42*, 520–528. [[CrossRef](#)]
119. Goff, H.D.; Repin, N.; Fabek, H.; El Khoury, D.; Gidley, M.J. Dietary fibre for glycaemia control: Towards a mechanistic understanding. *Bioact. Carbohydr. Diet. Fibre* **2018**, *14*, 39–53. [[CrossRef](#)]
120. Little, T.J.; Doran, S.; Meyer, J.H.; Smout, A.J.; O'Donovan, D.G.; Wu, K.-L.; Jones, K.L.; Wishart, J.; Rayner, C.K.; Horowitz, M. The release of GLP-1 and ghrelin, but not GIP and CCK, by glucose is dependent upon the length of small intestine exposed. *Am. J. Physiol.-Endocrinol. Metab.* **2006**, *291*, E647–E655. [[CrossRef](#)]
121. Esposito, K.; Pontillo, A.; Di Palo, C.; Giugliano, G.; Masella, M.; Marfella, R.; Giugliano, D. Effect of weight loss and lifestyle changes on vascular inflammatory markers in obese women: A randomized trial. *Jama* **2003**, *289*, 1799–1804. [[CrossRef](#)] [[PubMed](#)]
122. Galisteo, M.; Sanchez, M.; Vera, R.; González, M.; Anguera, A.; Duarte, J.; Zarzuelo, A. A diet supplemented with husks of *Plantago ovata* reduces the development of endothelial dysfunction, hypertension, and obesity by affecting adiponectin and TNF- $\alpha$  in obese Zucker rats. *J. Nutr.* **2005**, *135*, 2399–2404. [[CrossRef](#)] [[PubMed](#)]
123. Säemann, M.D.; Böhmig, G.A.; Österreicher, C.H.; Burtscher, H.; Parolini, O.; Diakos, C.; Stöckl, J.; Hörl, W.H.; Zlabinger, G.J. Anti-inflammatory effects of sodium butyrate on human monocytes: Potent inhibition of IL-12 and up-regulation of IL-10 production. *FASEB J.* **2000**, *14*, 2380–2382. [[CrossRef](#)] [[PubMed](#)]
124. Segain, J.; De La Blétière, D.R.; Bourreille, A.; Leray, V.; Gervois, N.; Rosales, C.; Ferrier, L.; Bonnet, C.; Blottiere, H.; Galmiche, J. Butyrate inhibits inflammatory responses through NF $\kappa$ B inhibition: Implications for Crohn's disease. *Gut* **2000**, *47*, 397–403. [[CrossRef](#)]
125. Gautier-Stein, A.; Mithieux, G. Intestinal gluconeogenesis: Metabolic benefits make sense in the light of evolution. *Nat. Rev. Gastroenterol. Hepatol.* **2023**, *20*, 183–194. [[CrossRef](#)] [[PubMed](#)]
126. Soty, M.; Gautier-Stein, A.; Rajas, F.; Mithieux, G. Gut-brain glucose signaling in energy homeostasis. *Cell Metab.* **2017**, *25*, 1231–1242. [[CrossRef](#)]

127. De Vadder, F.; Kovatcheva-Datchary, P.; Goncalves, D.; Vinera, J.; Zitoun, C.; Duchampt, A.; Bäckhed, F.; Mithieux, G. Microbiota-generated metabolites promote metabolic benefits via gut-brain neural circuits. *Cell* **2014**, *156*, 84–96. [[CrossRef](#)]
128. Gulliford, M.; Ukoumunne, O. Determinants of glycated haemoglobin in the general population: Associations with diet, alcohol and cigarette smoking. *Eur. J. Clin. Nutr.* **2001**, *55*, 615–623. [[CrossRef](#)]
129. Mayer, E.J.; Newman, B.; Quesenberry, C.P., Jr.; Selby, J.V. Usual dietary fat intake and insulin concentrations in healthy women twins. *Diabetes Care* **1993**, *16*, 1459–1469. [[CrossRef](#)]
130. Harding, A.-H.; Sargeant, L.A.; Welch, A.; Oakes, S.; Luben, R.N.; Bingham, S.; Day, N.E.; Khaw, K.-T.; Wareham, N.J. Fat consumption and HbA1c levels: The EPIC-Norfolk study. *Diabetes Care* **2001**, *24*, 1911–1916. [[CrossRef](#)]
131. Marshall, J.A.; Hoag, S.; Shetterly, S.; Hamman, R.F. Dietary fat predicts conversion from impaired glucose tolerance to NIDDM: The San Luis Valley Diabetes Study. *Diabetes Care* **1994**, *17*, 50–56. [[CrossRef](#)] [[PubMed](#)]
132. Feskens, E.J.; Virtanen, S.M.; Räsänen, L.; Tuomilehto, J.; Stengård, J.; Pekkanen, J.; Nissinen, A.; Kromhout, D. 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* **1995**, *18*, 1104–1112. [[CrossRef](#)] [[PubMed](#)]
133. Marshall, J.; Bessesen, D.; Hamman, R. High saturated fat and low starch and fibre are associated with hyperinsulinaemia in a non-diabetic population: The San Luis Valley Diabetes Study. *Diabetologia* **1997**, *40*, 430–438. [[CrossRef](#)]
134. Feskens, E.J.; Loeber, J.G.; Kromhout, D. Diet and physical activity as determinants of hyperinsulinemia: The Zutphen Elderly Study. *Am. J. Epidemiol.* **1994**, *140*, 350–360. [[CrossRef](#)] [[PubMed](#)]
135. Riccardi, G.; Rivellese, A.A. Dietary treatment of the metabolic syndrome—The optimal diet. *Br. J. Nutr.* **2000**, *83*, S143–S148. [[CrossRef](#)]
136. Samuel, V.T.; Shulman, G.I. Mechanisms for insulin resistance: Common threads and missing links. *Cell* **2012**, *148*, 852–871. [[CrossRef](#)]
137. Montgomery, M.K.; Osborne, B.; Brown, S.H.; Small, L.; Mitchell, T.W.; Cooney, G.J.; Turner, N. Contrasting metabolic effects of medium-versus long-chain fatty acids in skeletal muscle[S]. *J. Lipid Res.* **2013**, *54*, 3322–3333. [[CrossRef](#)]
138. Turner, N.; Hariharan, K.; TidAng, J.; Frangioudakis, G.; Beale, S.M.; Wright, L.E.; Zeng, X.Y.; Leslie, S.J.; Li, J.-Y.; Kraegen, E.W. Enhancement of muscle mitochondrial oxidative capacity and alterations in insulin action are lipid species dependent: Potent tissue-specific effects of medium-chain fatty acids. *Diabetes* **2009**, *58*, 2547–2554. [[CrossRef](#)]
139. St-Onge, M.P.; Ross, R.; Parsons, W.D.; Jones, P.J. Medium-chain triglycerides increase energy expenditure and decrease adiposity in overweight men. *Obes. Res.* **2003**, *11*, 395–402. [[CrossRef](#)]
140. Han, J.; Hamilton, J.A.; Kirkland, J.L.; Corkey, B.E.; Guo, W. Medium-chain oil reduces fat mass and down-regulates expression of adipogenic genes in rats. *Obes. Res.* **2003**, *11*, 734–744. [[CrossRef](#)]
141. Canfora, E.E.; Jocken, J.W.; Blaak, E.E. Short-chain fatty acids in control of body weight and insulin sensitivity. *Nat. Rev. Endocrinol.* **2015**, *11*, 577–591. [[CrossRef](#)]
142. Tan, J.; McKenzie, C.; Potamitis, M.; Thorburn, A.N.; Mackay, C.R.; Macia, L. The role of short-chain fatty acids in health and disease. *Adv. Immunol.* **2014**, *121*, 91–119. [[PubMed](#)]
143. Glass, C.K.; Olefsky, J.M. Inflammation and lipid signaling in the etiology of insulin resistance. *Cell Metab.* **2012**, *15*, 635–645. [[CrossRef](#)]
144. Vessby, B.; Uusitupa, M.; Hermansen, K.; Riccardi, G.; Rivellese, A.A.; Tapsell, L.C.; Nälsén, C.; Berglund, L.; Louheranta, A.; Rasmussen, B. Substituting dietary saturated for monounsaturated fat impairs insulin sensitivity in healthy men and women: The KANWU Study. *Diabetologia* **2001**, *44*, 312–319. [[CrossRef](#)]
145. Li, Y.; Lu, Z.; Ru, J.H.; Lopes-Virella, M.F.; Lyons, T.J.; Huang, Y. Saturated fatty acid combined with lipopolysaccharide stimulates a strong inflammatory response in hepatocytes in vivo and in vitro. *Am. J. Physiol.-Endocrinol. Metab.* **2018**, *315*, E745–E757. [[CrossRef](#)] [[PubMed](#)]
146. Nguyen, M.A.; Favelyukis, S.; Nguyen, A.-K.; Reichart, D.; Scott, P.A.; Jenn, A.; Liu-Bryan, R.; Glass, C.K.; Neels, J.G.; Olefsky, J.M. A subpopulation of macrophages infiltrates hypertrophic adipose tissue and is activated by free fatty acids via Toll-like receptors 2 and 4 and JNK-dependent pathways. *J. Biol. Chem.* **2007**, *282*, 35279–35292. [[CrossRef](#)]
147. Bradley, R.L.; Fisher, F.M.; Maratos-Flier, E. Dietary Fatty Acids Differentially Regulate Production of TNF- $\alpha$  and IL-10 by Murine 3T3-L1 Adipocytes. *Obesity* **2008**, *16*, 938–944. [[CrossRef](#)] [[PubMed](#)]
148. Lee, J.Y.; Sohn, K.H.; Rhee, S.H.; Hwang, D. Saturated fatty acids, but not unsaturated fatty acids, induce the expression of cyclooxygenase-2 mediated through Toll-like receptor 4. *J. Biol. Chem.* **2001**, *276*, 16683–16689. [[CrossRef](#)] [[PubMed](#)]
149. Schaeffler, A.; Gross, P.; Buettner, R.; Bollheimer, C.; Buechler, C.; Neumeier, M.; Kopp, A.; Schoelmerich, J.; Falk, W. Fatty acid-induced induction of Toll-like receptor-4/nuclear factor- $\kappa$ B pathway in adipocytes links nutritional signalling with innate immunity. *Immunology* **2009**, *126*, 233–245. [[CrossRef](#)]
150. Senn, J.J. Toll-like receptor-2 is essential for the development of palmitate-induced insulin resistance in myotubes. *J. Biol. Chem.* **2006**, *281*, 26865–26875. [[CrossRef](#)]
151. Shi, H.; Kokoeva, M.V.; Inouye, K.; Tzameli, I.; Yin, H.; Flier, J.S. TLR4 links innate immunity and fatty acid-induced insulin resistance. *J. Clin. Investig.* **2006**, *116*, 3015–3025. [[CrossRef](#)] [[PubMed](#)]
152. Seimon, T.A.; Nadolski, M.J.; Liao, X.; Magallon, J.; Nguyen, M.; Feric, N.T.; Koschinsky, M.L.; Harkewicz, R.; Witztum, J.L.; Tsimikas, S. Atherogenic lipids and lipoproteins trigger CD36-TLR2-dependent apoptosis in macrophages undergoing endoplasmic reticulum stress. *Cell Metab.* **2010**, *12*, 467–482. [[CrossRef](#)]



153. Stewart, C.R.; Stuart, L.M.; Wilkinson, K.; Van Gils, J.M.; Deng, J.; Halle, A.; Rayner, K.J.; Boyer, L.; Zhong, R.; Frazier, W.A. CD36 ligands promote sterile inflammation through assembly of a Toll-like receptor 4 and 6 heterodimer. *Nat. Immunol.* **2010**, *11*, 155–161. [[CrossRef](#)] [[PubMed](#)]
154. Wong, S.W.; Kwon, M.-J.; Choi, A.M.; Kim, H.-P.; Nakahira, K.; Hwang, D.H. Fatty acids modulate Toll-like receptor 4 activation through regulation of receptor dimerization and recruitment into lipid rafts in a reactive oxygen species-dependent manner. *J. Biol. Chem.* **2009**, *284*, 27384–27392. [[CrossRef](#)]
155. Holzer, R.G.; Park, E.-J.; Li, N.; Tran, H.; Chen, M.; Choi, C.; Solinas, G.; Karin, M. Saturated fatty acids induce c-Src clustering within membrane subdomains, leading to JNK activation. *Cell* **2011**, *147*, 173–184. [[CrossRef](#)]
156. Arkan, M.C.; Hevener, A.L.; Greten, F.R.; Maeda, S.; Li, Z.-W.; Long, J.M.; Wynshaw-Boris, A.; Poli, G.; Olefsky, J.; Karin, M. IKK- $\beta$  links inflammation to obesity-induced insulin resistance. *Nat. Med.* **2005**, *11*, 191–198. [[CrossRef](#)] [[PubMed](#)]
157. Hotamisligil, G.S.; Peraldi, P.; Budavari, A.; Ellis, R.; White, M.F.; Spiegelman, B.M. IRS-1-mediated inhibition of insulin receptor tyrosine kinase activity in TNF- $\alpha$ -and obesity-induced insulin resistance. *Science* **1996**, *271*, 665–670. [[CrossRef](#)] [[PubMed](#)]
158. Wen, H.; Gris, D.; Lei, Y.; Jha, S.; Zhang, L.; Huang, M.T.-H.; Brickey, W.J.; Ting, J.P. Fatty acid-induced NLRP3-ASC inflammasome activation interferes with insulin signaling. *Nat. Immunol.* **2011**, *12*, 408–415. [[CrossRef](#)]
159. Samuel, V.T.; Petersen, K.F.; Shulman, G.I. Lipid-induced insulin resistance: Unravelling the mechanism. *Lancet* **2010**, *375*, 2267–2277. [[CrossRef](#)]
160. Kumashiro, N.; Erion, D.M.; Zhang, D.; Kahn, M.; Beddow, S.A.; Chu, X.; Still, C.D.; Gerhard, G.S.; Han, X.; Dziura, J. Cellular mechanism of insulin resistance in nonalcoholic fatty liver disease. *Proc. Natl. Acad. Sci. USA* **2011**, *108*, 16381–16385. [[CrossRef](#)]
161. Stratford, S.; Hoehn, K.L.; Liu, F.; Summers, S.A. Regulation of insulin action by ceramide: Dual mechanisms linking ceramide accumulation to the inhibition of Akt/protein kinase B. *J. Biol. Chem.* **2004**, *279*, 36608–36615. [[CrossRef](#)] [[PubMed](#)]
162. Ussher, J.R.; Koves, T.R.; Cadete, V.J.; Zhang, L.; Jaswal, J.S.; Swyrd, S.J.; Lopaschuk, D.G.; Proctor, S.D.; Keung, W.; Muoio, D.M. Inhibition of de novo ceramide synthesis reverses diet-induced insulin resistance and enhances whole-body oxygen consumption. *Diabetes* **2010**, *59*, 2453–2464. [[CrossRef](#)] [[PubMed](#)]
163. Ozcan, U.; Cao, Q.; Yilmaz, E.; Lee, A.-H.; Iwakoshi, N.N.; Ozdelen, E.; Tuncman, G.; Gorgun, C.; Glimcher, L.H.; Hotamisligil, G.S. Endoplasmic reticulum stress links obesity, insulin action, and type 2 diabetes. *Science* **2004**, *306*, 457–461. [[CrossRef](#)] [[PubMed](#)]
164. Ozcan, U.; Yilmaz, E.; Ozcan, L.; Furuhashi, M.; Vaillancourt, E.; Smith, R.O.; Gorgun, C.Z.; Hotamisligil, G.K.S. Chemical chaperones reduce ER stress and restore glucose homeostasis in a mouse model of type 2 diabetes. *Science* **2006**, *313*, 1137–1140. [[CrossRef](#)] [[PubMed](#)]
165. Minville-Walz, M.; Pierre, A.-S.; Pichon, L.; Bellenger, S.; Fèvre, C.; Bellenger, J.; Tessier, C.; Narce, M.; Rialland, M. Inhibition of stearoyl-CoA desaturase 1 expression induces CHOP-dependent cell death in human cancer cells. *PLoS ONE* **2010**, *5*, e14363. [[CrossRef](#)]
166. Feng, B.; Yao, P.M.; Li, Y.; Devlin, C.M.; Zhang, D.; Harding, H.P.; Sweeney, M.; Rong, J.X.; Kuriakose, G.; Fisher, E.A. The endoplasmic reticulum is the site of cholesterol-induced cytotoxicity in macrophages. *Nat. Cell Biol.* **2003**, *5*, 781–792. [[CrossRef](#)]
167. Cunha, D.A.; Hekerman, P.; Ladrière, L.; Bazarra-Castro, A.; Ortis, F.; Wakeham, M.C.; Moore, F.; Rasschaert, J.; Cardozo, A.K.; Bellomo, E. Initiation and execution of lipotoxic ER stress in pancreatic  $\beta$ -cells. *J. Cell Sci.* **2008**, *121*, 2308–2318. [[CrossRef](#)]
168. Lam, T.K.; Pocai, A.; Gutierrez-Juarez, R.; Obici, S.; Bryan, J.; Aguilar-Bryan, L.; Schwartz, G.J.; Rossetti, L. Hypothalamic sensing of circulating fatty acids is required for glucose homeostasis. *Nat. Med.* **2005**, *11*, 320–327. [[CrossRef](#)]
169. Heni, M.; Wagner, R.; Kullmann, S.; Gancheva, S.; Roden, M.; Peter, A.; Stefan, N.; Preissl, H.; Häring, H.-U.; Fritsche, A. Hypothalamic and striatal insulin action suppresses endogenous glucose production and may stimulate glucose uptake during hyperinsulinemia in lean but not in overweight men. *Diabetes* **2017**, *66*, 1797–1806. [[CrossRef](#)]
170. Ono, H.; Pocai, A.; Wang, Y.; Sakoda, H.; Asano, T.; Backer, J.M.; Schwartz, G.J.; Rossetti, L. Activation of hypothalamic S6 kinase mediates diet-induced hepatic insulin resistance in rats. *J. Clin. Investig.* **2008**, *118*, 2959–2968. [[CrossRef](#)]
171. Benoit, S.C.; Kemp, C.J.; Elias, C.F.; Abplanalp, W.; Herman, J.P.; Migrenne, S.; Lefevre, A.-L.; Cruciani-Guglielmacci, C.; Magnan, C.; Yu, F. Palmitic acid mediates hypothalamic insulin resistance by altering PKC- $\theta$  subcellular localization in rodents. *J. Clin. Investig.* **2009**, *119*, 2577–2589. [[CrossRef](#)] [[PubMed](#)]
172. De Souza, C.T.; Araujo, E.P.; Bordin, S.; Ashimine, R.; Zollner, R.L.; Boschero, A.C.; Saad, M.J.; Velloso, L.A. Consumption of a fat-rich diet activates a proinflammatory response and induces insulin resistance in the hypothalamus. *Endocrinology* **2005**, *146*, 4192–4199. [[CrossRef](#)] [[PubMed](#)]
173. Zhang, X.; Zhang, G.; Zhang, H.; Karin, M.; Bai, H.; Cai, D. Hypothalamic IKK $\beta$ /NF- $\kappa$ B and ER stress link overnutrition to energy imbalance and obesity. *Cell* **2008**, *135*, 61–73. [[CrossRef](#)] [[PubMed](#)]
174. Ono, H. Molecular mechanisms of hypothalamic insulin resistance. *Int. J. Mol. Sci.* **2019**, *20*, 1317. [[CrossRef](#)] [[PubMed](#)]
175. Milanski, M.; Degasperis, G.; Coope, A.; Morari, J.; Denis, R.; Cintra, D.E.; Tsukumo, D.M.; Anhe, G.; Amaral, M.E.; Takahashi, H.K. Saturated fatty acids produce an inflammatory response predominantly through the activation of TLR4 signaling in hypothalamus: Implications for the pathogenesis of obesity. *J. Neurosci.* **2009**, *29*, 359–370. [[CrossRef](#)]
176. Clarke, S.D. Polyunsaturated fatty acid regulation of gene transcription: A mechanism to improve energy balance and insulin resistance. *Br. J. Nutr.* **2000**, *83*, S59–S66. [[CrossRef](#)]



177. Ramel, A.; Martinez, A.; Kiely, M.; Morais, G.; Bandarra, N.; Thorsdottir, I. Beneficial effects of long-chain n-3 fatty acids included in an energy-restricted diet on insulin resistance in overweight and obese European young adults. *Diabetologia* **2008**, *51*, 1261–1268. [[CrossRef](#)]
178. Huang, T.; Wahlqvist, M.L.; Xu, T.; Xu, A.; Zhang, A.; Li, D. Increased plasma n-3 polyunsaturated fatty acid is associated with improved insulin sensitivity in type 2 diabetes in China. *Mol. Nutr. Food Res.* **2010**, *54*, S112–S119. [[CrossRef](#)]
179. Lee, J.Y.; Plakidas, A.; Lee, W.H.; Heikkinen, A.; Chanmugam, P.; Bray, G.; Hwang, D.H. Differential modulation of Toll-like receptors by fatty acids: Preferential inhibition by n-3 polyunsaturated fatty acids. *J. Lipid Res.* **2003**, *44*, 479–486. [[CrossRef](#)]
180. Talukdar, S.; Bae, E.J.; Imamura, T.; Morinaga, H.; Fan, W.; Li, P.; Lu, W.J.; Watkins, S.M.; Olefsky, J.M. GPR120 is an omega-3 fatty acid receptor mediating potent anti-inflammatory and insulin-sensitizing effects. *Cell* **2010**, *142*, 687–698.
181. Serhan, C.N.; Chiang, N. Endogenous pro-resolving and anti-inflammatory lipid mediators: A new pharmacologic genus. *Br. J. Pharmacol.* **2008**, *153*, S200–S215. [[CrossRef](#)]
182. Serhan, C.N.; Chiang, N.; Van Dyke, T.E. Resolving inflammation: Dual anti-inflammatory and pro-resolution lipid mediators. *Nat. Rev. Immunol.* **2008**, *8*, 349–361. [[CrossRef](#)] [[PubMed](#)]
183. Cao, H.; Gerhold, K.; Mayers, J.R.; Wiest, M.M.; Watkins, S.M.; Hotamisligil, G.S. Identification of a lipokine, a lipid hormone linking adipose tissue to systemic metabolism. *Cell* **2008**, *134*, 933–944. [[CrossRef](#)] [[PubMed](#)]
184. Beysen, C.; Karpe, F.; Fielding, B.; Clark, A.; Levy, J.; Frayn, K. Interaction between specific fatty acids, GLP-1 and insulin secretion in humans. *Diabetologia* **2002**, *45*, 1533–1541. [[PubMed](#)]
185. Thomsen, C.; Rasmussen, O.; Lousen, T.; Holst, J.J.; Fenselau, S.; Schrezenmeier, J.; Hermansen, K. Differential effects of saturated and monounsaturated fatty acids on postprandial lipemia and incretin responses in healthy subjects. *Am. J. Clin. Nutr.* **1999**, *69*, 1135–1143. [[CrossRef](#)] [[PubMed](#)]
186. Gentilcore, D.; Chaikomin, R.; Jones, K.L.; Russo, A.; Feinle-Bisset, C.; Wishart, J.M.; Rayner, C.K.; Horowitz, M. Effects of fat on gastric emptying of and the glycemic, insulin, and incretin responses to a carbohydrate meal in type 2 diabetes. *J. Clin. Endocrinol. Metab.* **2006**, *91*, 2062–2067. [[CrossRef](#)] [[PubMed](#)]
187. Rocca, A.S.; Brubaker, P.L. Stereospecific effects of fatty acids on proglucagon-derived peptide secretion in fetal rat intestinal cultures. *Endocrinology* **1995**, *136*, 5593–5599. [[CrossRef](#)]
188. Peters, S.A.; Muntner, P.; Woodward, M. Sex differences in the prevalence of, and trends in, cardiovascular risk factors, treatment, and control in the United States, 2001 to 2016. *Circulation* **2019**, *139*, 1025–1035. [[CrossRef](#)]
189. Cho, N.H.; Shaw, J.; Karuranga, S.; Huang, Y.; da Rocha Fernandes, J.; Ohlrogge, A.; Malanda, B. IDF Diabetes Atlas: Global estimates of diabetes prevalence for 2017 and projections for 2045. *Diabetes Res. Clin. Pract.* **2018**, *138*, 271–281. [[CrossRef](#)]
190. Riant, E.; Waget, A.; Cogo, H.; Arnal, J.-F.; Burcelin, R.; Gourdy, P. Estrogens protect against high-fat diet-induced insulin resistance and glucose intolerance in mice. *Endocrinology* **2009**, *150*, 2109–2117. [[CrossRef](#)]
191. Xie, C.; Huang, W.; Sun, Y.; Xiang, C.; Trahair, L.; Jones, K.L.; Horowitz, M.; Rayner, C.K.; Wu, T. Disparities in the Glycemic and Incretin Responses to Intraduodenal Glucose Infusion Between Healthy Young Men and Women. *J. Clin. Endocrinol. Metab.* **2023**, *108*, e712–e719. [[CrossRef](#)] [[PubMed](#)]
192. Bauer, I.; Hughes, M.; Rowsell, R.; Cockerell, R.; Pipingas, A.; Crewther, S.; Crewther, D. Omega-3 supplementation improves cognition and modifies brain activation in young adults. *Hum. Psychopharmacol. Clin. Exp.* **2014**, *29*, 133–144. [[CrossRef](#)] [[PubMed](#)]
193. Witte, A.V.; Kerti, L.; Hermannstädter, H.M.; Fiebach, J.B.; Schreiber, S.J.; Schuchardt, J.P.; Hahn, A.; Flöel, A. Long-chain omega-3 fatty acids improve brain function and structure in older adults. *Cereb. Cortex* **2014**, *24*, 3059–3068. [[CrossRef](#)] [[PubMed](#)]
194. Kiecolt-Glaser, J.K.; Belury, M.A.; Andridge, R.; Malarkey, W.B.; Hwang, B.S.; Glaser, R. Omega-3 supplementation lowers inflammation in healthy middle-aged and older adults: A randomized controlled trial. *Brain Behav. Immun.* **2012**, *26*, 988–995. [[CrossRef](#)]
195. Feskens, E.J.; Bowles, C.H.; Kromhout, D. Inverse association between fish intake and risk of glucose intolerance in normoglycemic elderly men and women. *Diabetes Care* **1991**, *14*, 935–941. [[CrossRef](#)]
196. Halton, T.L.; Hu, F.B. The effects of high protein diets on thermogenesis, satiety and weight loss: A critical review. *J. Am. Coll. Nutr.* **2004**, *23*, 373–385. [[CrossRef](#)]
197. Hu, F.B. Protein, body weight, and cardiovascular health. *Am. J. Clin. Nutr.* **2005**, *82*, 242S–247S. [[CrossRef](#)]
198. Mithieux, G.; Misery, P.; Magnan, C.; Pillot, B.; Gautier-Stein, A.; Bernard, C.; Rajas, F.; Zitoun, C. Portal sensing of intestinal gluconeogenesis is a mechanistic link in the diminution of food intake induced by diet protein. *Cell Metab.* **2005**, *2*, 321–329. [[CrossRef](#)]
199. Penhoat, A.; Mutel, E.; Amigo-Correig, M.; Pillot, B.; Stefanutti, A.; Rajas, F.; Mithieux, G. Protein-induced satiety is abolished in the absence of intestinal gluconeogenesis. *Physiol. Behav.* **2011**, *105*, 89–93. [[CrossRef](#)]
200. Spiller, G.A.; Jensen, C.D.; Pattison, T.; Chuck, C.S.; Whittam, J.H.; Scala, J. Effect of protein dose on serum glucose and insulin response to sugars. *Am. J. Clin. Nutr.* **1987**, *46*, 474–480. [[CrossRef](#)]
201. Wu, T.; Little, T.J.; Bound, M.J.; Borg, M.; Zhang, X.; Deacon, C.F.; Horowitz, M.; Jones, K.L.; Rayner, C.K. A protein preload enhances the glucose-lowering efficacy of vildagliptin in type 2 diabetes. *Diabetes Care* **2016**, *39*, 511–517. [[CrossRef](#)] [[PubMed](#)]
202. Ma, J.; Stevens, J.E.; Cukier, K.; Maddox, A.F.; Wishart, J.M.; Jones, K.L.; Clifton, P.M.; Horowitz, M.; Rayner, C.K. Effects of a protein preload on gastric emptying, glycemia, and gut hormones after a carbohydrate meal in diet-controlled type 2 diabetes. *Diabetes Care* **2009**, *32*, 1600–1602. [[CrossRef](#)] [[PubMed](#)]

203. Gannon, M.C.; Nuttall, F.Q.; Saeed, A.; Jordan, K.; Hoover, H. An increase in dietary protein improves the blood glucose response in persons with type 2 diabetes. *Am. J. Clin. Nutr.* **2003**, *78*, 734–741. [[CrossRef](#)] [[PubMed](#)]
204. Linn, T.; Santosa, B.; Grönemeyer, D.; Aygen, S.; Scholz, N.; Busch, M.; Bretzel, R. Effect of long-term dietary protein intake on glucose metabolism in humans. *Diabetologia* **2000**, *43*, 1257–1265. [[CrossRef](#)]
205. Linn, T.; Geyer, R.; Prassek, S.; Laube, H. Effect of dietary protein intake on insulin secretion and glucose metabolism in insulin-dependent diabetes mellitus. *J. Clin. Endocrinol. Metab.* **1996**, *81*, 3938–3943.
206. Linn, T.; Strate, C.; Schneider, K. Diet promotes  $\beta$ -cell loss by apoptosis in prediabetic nonobese diabetic mice. *Endocrinology* **1999**, *140*, 3767–3773. [[CrossRef](#)]
207. Lavigne, C.; Marette, A.; Jacques, H. Cod and soy proteins compared with casein improve glucose tolerance and insulin sensitivity in rats. *Am. J. Physiol.-Endocrinol. Metab.* **2000**, *278*, E491–E500. [[CrossRef](#)]
208. Malik, V.S.; Li, Y.; Tobias, D.K.; Pan, A.; Hu, F.B. Dietary protein intake and risk of type 2 diabetes in US men and women. *Am. J. Epidemiol.* **2016**, *183*, 715–728. [[CrossRef](#)]
209. Bergeron, N.; Jacques, H. Influence of fish protein as compared to casein and soy protein on serum and liver lipids, and serum lipoprotein cholesterol levels in the rabbit. *Atherosclerosis* **1989**, *78*, 113–121. [[CrossRef](#)]
210. Lavigne, C.; Tremblay, F.; Asselin, G.; Jacques, H.; Marette, A. Prevention of skeletal muscle insulin resistance by dietary cod protein in high fat-fed rats. *Am. J. Physiol.-Endocrinol. Metab.* **2001**, *281*, E62–E71. [[CrossRef](#)]
211. Newgard, C.B.; An, J.; Bain, J.R.; Muehlbauer, M.J.; Stevens, R.D.; Lien, L.F.; Haqq, A.M.; Shah, S.H.; Arlotto, M.; Slentz, C.A. A branched-chain amino acid-related metabolic signature that differentiates obese and lean humans and contributes to insulin resistance. *Cell Metab.* **2009**, *9*, 311–326. [[CrossRef](#)] [[PubMed](#)]
212. Krebs, M.; Krssak, M.; Bernroider, E.; Anderwald, C.; Brehm, A.; Meyerspeer, M.; Nowotny, P.; Roth, E.; Waldhäusl, W.; Roden, M. Mechanism of amino acid-induced skeletal muscle insulin resistance in humans. *Diabetes* **2002**, *51*, 599–605. [[CrossRef](#)] [[PubMed](#)]
213. Tremblay, F.; Krebs, M.; Dombrowski, L.; Brehm, A.; Bernroider, E.; Roth, E.; Nowotny, P.; Waldhäusl, W.; Marette, A.; Roden, M. Overactivation of S6 kinase 1 as a cause of human insulin resistance during increased amino acid availability. *Diabetes* **2005**, *54*, 2674–2684. [[CrossRef](#)] [[PubMed](#)]
214. Tremblay, F.; Marette, A. Amino acid and insulin signaling via the mTOR/p70 S6 kinase pathway: A negative feedback mechanism leading to insulin resistance in skeletal muscle cells. *J. Biol. Chem.* **2001**, *276*, 38052–38060. [[CrossRef](#)]
215. Takano, A.; Usui, I.; Haruta, T.; Kawahara, J.; Uno, T.; Iwata, M.; Kobayashi, M. Mammalian target of rapamycin pathway regulates insulin signaling via subcellular redistribution of insulin receptor substrate 1 and integrates nutritional signals and metabolic signals of insulin. *Mol. Cell. Biol.* **2001**, *21*, 5050–5062. [[CrossRef](#)]
216. Patti, M.-E.; Brambilla, E.; Luzi, L.; Landaker, E.J.; Kahn, C.R. Bidirectional modulation of insulin action by amino acids. *J. Clin. Invest.* **1998**, *101*, 1519–1529. [[CrossRef](#)]
217. Ohneda, A.; Parada, E.; Eisentraut, A.M.; Unger, R.H. Characterization of response of circulating glucagon to intraduodenal and intravenous administration of amino acids. *J. Clin. Invest.* **1968**, *47*, 2305–2322. [[CrossRef](#)]
218. Zhao, H.; Zhang, F.; Sun, D.; Wang, X.; Zhang, X.; Zhang, J.; Yan, F.; Huang, C.; Xie, H.; Lin, C. Branched-chain amino acids exacerbate obesity-related hepatic glucose and lipid metabolic disorders via attenuating Akt2 signaling. *Diabetes* **2020**, *69*, 1164–1177. [[CrossRef](#)]
219. Würtz, P.; Soinen, P.; Kangas, A.J.; Rönnemaa, T.; Lehtimäki, T.; Kähönen, M.; Viikari, J.S.; Raitakari, O.T.; Ala-Korpela, M. Branched-chain and aromatic amino acids are predictors of insulin resistance in young adults. *Diabetes Care* **2013**, *36*, 648–655. [[CrossRef](#)]
220. Phielix, E.; Jelenik, T.; Nowotny, P.; Szendroedi, J.; Roden, M. Reduction of non-esterified fatty acids improves insulin sensitivity and lowers oxidative stress, but fails to restore oxidative capacity in type 2 diabetes: A randomised clinical trial. *Diabetologia* **2014**, *57*, 572–581. [[CrossRef](#)]
221. Vanweert, F.; Schrauwen, P.; Phielix, E. Role of branched-chain amino acid metabolism in the pathogenesis of obesity and type 2 diabetes-related metabolic disturbances BCAA metabolism in type 2 diabetes. *Nutr. Diabetes* **2022**, *12*, 35. [[CrossRef](#)] [[PubMed](#)]
222. Vanweert, F.; de Ligt, M.; Hoeks, J.; Hesselink, M.K.; Schrauwen, P.; Phielix, E. Elevated plasma branched-chain amino acid levels correlate with type 2 diabetes-related metabolic disturbances. *J. Clin. Endocrinol. Metab.* **2021**, *106*, e1827–e1836. [[CrossRef](#)] [[PubMed](#)]
223. Newgard, C.B. Interplay between lipids and branched-chain amino acids in development of insulin resistance. *Cell Metab.* **2012**, *15*, 606–614. [[CrossRef](#)] [[PubMed](#)]
224. Aguer, C.; McCain, C.S.; Knotts, T.A.; Thrush, A.B.; Ono-Moore, K.; McPherson, R.; Dent, R.; Hwang, D.H.; Adams, S.H.; Harper, M.-E. Acylcarnitines: Potential implications for skeletal muscle insulin resistance. *FASEB J.* **2015**, *29*, 336. [[CrossRef](#)]
225. Koves, T.R.; Ussher, J.R.; Noland, R.C.; Slentz, D.; Mosedale, M.; Ilkayeva, O.; Bain, J.; Stevens, R.; Dyck, J.R.; Newgard, C.B. Mitochondrial overload and incomplete fatty acid oxidation contribute to skeletal muscle insulin resistance. *Cell Metab.* **2008**, *7*, 45–56. [[CrossRef](#)]
226. Adeva, M.M.; Calviño, J.; Souto, G.; Donapetry, C. Insulin resistance and the metabolism of branched-chain amino acids in humans. *Amino Acids* **2012**, *43*, 171–181. [[CrossRef](#)]
227. Li, T.; Zhang, Z.; Kolwicz, S.C.; Abell, L.; Roe, N.D.; Kim, M.; Zhou, B.; Cao, Y.; Ritterhoff, J.; Gu, H. Defective branched-chain amino acid catabolism disrupts glucose metabolism and sensitizes the heart to ischemia-reperfusion injury. *Cell Metab.* **2017**, *25*, 374–385. [[CrossRef](#)] [[PubMed](#)]

228. Drábková, P.; Šanderová, J.; Kovařík, J.; Kanďár, R. An assay of selected serum amino acids in patients with type 2 diabetes mellitus. *Adv. Clin. Exp. Med.* **2015**, *24*, 447–451. [[CrossRef](#)]
229. Wang-Sattler, R.; Yu, Z.; Herder, C.; Messias, A.C.; Floegel, A.; He, Y.; Heim, K.; Campillos, M.; Holzapfel, C.; Thorand, B. Novel biomarkers for pre-diabetes identified by metabolomics. *Mol. Syst. Biol.* **2012**, *8*, 615. [[CrossRef](#)]
230. Floegel, A.; Stefan, N.; Yu, Z.; Mühlenbruch, K.; Drogan, D.; Joost, H.-G.; Fritsche, A.; Häring, H.-U.; Hrabě de Angelis, M.; Peters, A. Identification of serum metabolites associated with risk of type 2 diabetes using a targeted metabolomic approach. *Diabetes* **2013**, *62*, 639–648. [[CrossRef](#)]
231. Palmer, N.D.; Stevens, R.D.; Antinozzi, P.A.; Anderson, A.; Bergman, R.N.; Wagenknecht, L.E.; Newgard, C.B.; Bowden, D.W. Metabolomic profile associated with insulin resistance and conversion to diabetes in the Insulin Resistance Atherosclerosis Study. *J. Clin. Endocrinol. Metab.* **2015**, *100*, E463–E468. [[CrossRef](#)]
232. El-Hafidi, M.; Franco, M.; Ramírez, A.R.; Sosa, J.S.; Flores, J.A.P.; Acosta, O.L.; Salgado, M.C.; Cardoso-Saldaña, G. Glycine increases insulin sensitivity and glutathione biosynthesis and protects against oxidative stress in a model of sucrose-induced insulin resistance. *Oxidative Med. Cell. Longev.* **2018**, *2018*, 2101562. [[CrossRef](#)] [[PubMed](#)]
233. Piatti, P.; Monti, L.D.; Valsecchi, G.; Magni, F.; Setola, E.; Marchesi, F.; Galli-Kienle, M.; Pozza, G.; Alberti, K.G.M. Long-term oral L-arginine administration improves peripheral and hepatic insulin sensitivity in type 2 diabetic patients. *Diabetes Care* **2001**, *24*, 875–880. [[CrossRef](#)]
234. De Toro-Martín, J.; Arsenault, B.J.; Després, J.-P.; Vohl, M.-C. Precision nutrition: A review of personalized nutritional approaches for the prevention and management of metabolic syndrome. *Nutrients* **2017**, *9*, 913. [[CrossRef](#)] [[PubMed](#)]
235. Ferguson, L.R.; De Caterina, R.; Görman, U.; Allayee, H.; Kohlmeier, M.; Prasad, C.; Choi, M.S.; Curi, R.; De Luis, D.A.; Gil, Á. Guide and position of the international society of nutrigenetics/nutrigenomics on personalised nutrition: Part 1-fields of precision nutrition. *J. Nutr. Nutr.* **2016**, *9*, 12–27. [[CrossRef](#)] [[PubMed](#)]
236. Goni, L.; Cuervo, M.; Milagro, F.I.; Martínez, J.A. A genetic risk tool for obesity predisposition assessment and personalized nutrition implementation based on macronutrient intake. *Genes Nutr.* **2015**, *10*, 445. [[CrossRef](#)] [[PubMed](#)]
237. Rukh, G.; Sonestedt, E.; Melander, O.; Hedblad, B.; Wirfält, E.; Ericson, U.; Orho-Melander, M. Genetic susceptibility to obesity and diet intakes: Association and interaction analyses in the Malmö Diet and Cancer Study. *Genes Nutr.* **2013**, *8*, 535–547. [[CrossRef](#)]
238. Olsen, N.J.; Ångquist, L.; Larsen, S.C.; Linneberg, A.; Skaaby, T.; Husemoen, L.L.N.; Toft, U.; Tjønneland, A.; Halkjær, J.; Hansen, T. Interactions between genetic variants associated with adiposity traits and soft drinks in relation to longitudinal changes in body weight and waist circumference. *Am. J. Clin. Nutr.* **2016**, *104*, 816–826. [[CrossRef](#)]
239. Corella, D.; Tai, E.S.; Sorlí, J.V.; Chew, S.K.; Coltell, O.; Sotos-Prieto, M.; García-Rios, A.; Estruch, R.; Ordovas, J.M. Association between the APOA2 promoter polymorphism and body weight in Mediterranean and Asian populations: Replication of a gene-saturated fat interaction. *Int. J. Obes.* **2011**, *35*, 666–675. [[CrossRef](#)]
240. Cornelis, M.C.; El-Sohehy, A.; Campos, H. Genetic polymorphism of the adenosine A2A receptor is associated with habitual caffeine consumption. *Am. J. Clin. Nutr.* **2007**, *86*, 240–244. [[CrossRef](#)]
241. Brennan, L. Metabolomics in nutrition research—a powerful window into nutritional metabolism. *Essays Biochem.* **2016**, *60*, 451–458.
242. Le Chatelier, E.; Nielsen, T.; Qin, J.; Prifti, E.; Hildebrand, F.; Falony, G.; Almeida, M.; Arumugam, M.; Batto, J.-M.; Kennedy, S. Richness of human gut microbiome correlates with metabolic markers. *Nature* **2013**, *500*, 541–546. [[CrossRef](#)] [[PubMed](#)]
243. Bonder, M.J.; Kurilshikov, A.; Tigchelaar, E.F.; Mujagic, Z.; Imhann, F.; Vila, A.V.; Deelen, P.; Vatanen, T.; Schirmer, M.; Smeekens, S.P. The effect of host genetics on the gut microbiome. *Nat. Genet.* **2016**, *48*, 1407–1412. [[CrossRef](#)] [[PubMed](#)]
244. Jin, Q.; Black, A.; Kales, S.N.; Vatter, D.; Ruiz-Canela, M.; Sotos-Prieto, M. Metabolomics and microbiomes as potential tools to evaluate the effects of the Mediterranean diet. *Nutrients* **2019**, *11*, 207. [[CrossRef](#)] [[PubMed](#)]

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