# Insulin Resistance and Metabolic Syndrome

Subjects: Endocrinology & Metabolism

Contributor: Abdullah I. Aedh, Majed S. Alshahrani, Mohammed A. Huneif, Ian F. Pryme, Ramadhan Oruch

Insulin is the main metabolic regulator of fuel molecules in the diet, such as carbohydrates, lipids, and proteins. It does so by facilitating glucose influx from the circulation into the liver, adipose tissue, and skeletal myocytes. The outcome of which is subjected to glycogenesis in skeletal muscle and lipogenesis in adipose tissue, as well as in the liver. Metabolic syndrome is the congregation of abdominal obesity (visceral obesity), hypertension, hyperglycemia, hyperlipidemia (triglycerides), and low serum high-density lipoprotein (HDL). At least three of these criteria must exist for the diagnosis of this syndrome. Insulin resistance is indeed a component of this syndrome. When hyperglycemia falls below the threshold to diagnose diabetes mellitus, the condition is called prediabetes. Insulin resistance, prediabetes, and metabolic syndrome share a spectrum of an overlapping area, thus they are closely related conditions and are milestones of a spectrum of a huge metabolic disorder of energy utilization and storage. Metabolic syndrome is indeed a serious condition in that it is a potential risk factor for ischemic heart diseases and type 2 diabetes (T2D).

Keywords: type 2 diabetes ; gestational diabetes ; mitochondrial dysfunction ; autoimmunity ; gut microbiota ; reactive oxygen species

## 1. Type 2 Diabetes

Type 2 diabetes (T2D) is the end stage of the pathologic spectrum of metabolic syndrome, in which hyperlipidemia, low levels of high-density lipoprotein (HDL), and hypertension are also prominent features of the syndrome in the Western world [1]. The essential and first millstone of this metabolic disorder is IR. This may be accompanied by a relative reduction in insulin secretion in response to carbohydrate ingestion [2]. This phenomenon has been explained by relying on the hypothesis of improper responsiveness of insulin receptors to the insulin being released postprandially (2 h after eating). This type of diabetes is accepted as the most common subcategory within diabetes mellitus. Things are intermingled in a very complicated image in such a way that many individuals with this disorder demonstrate evidence of the prediabetes state, which is manifested by impaired glucose tolerance and increased fasting blood glucose [3]. To reverse or at least slow down the development cascade of T2D is possible by two important means: (1) changing the lifestyle, which includes adopting healthy nutritional habits and practicing regular bodily exercises, and (2) medications that can reduce glycogenolysis (by the liver) and decrease glucose absorption from the intestine, and thus improve insulin sensitivity [4]. As T2D is an inevitable consequence of neglected cases of IR, the most effective preventive measure health caregivers should consider when managing these individuals is providing strong advice to fight obesity. It is true that T2D has genetic predisposing factors, but environmental factors have a lot to say in this context [5]. Other environmental elements that can ignite diabetes mellitus include stress, sedentary life, bad dietary habits, and urbanization, as has been stated elsewhere in this work [6]. The consumption of trans and saturated fatty acids in addition to sweetened drinks (with sucrose) is among the prominent predisposing factors to developing T2D [7][8][9]. In general, foodstuffs characterized by having a high glycemic index (ranging between 70 and above) should be avoided, such as white rice; see **Table 1** [10][11][12][13].

**Table 1.** The glycemic indices (GIs) of different food and nutrients.

| Foodstuff and GI | Examples of Food |
| --- | --- |
| Food with a low GI range (55 or less) | Monosaccharides: fructose; tagatose.<br>Pulses (beans): black; kidney; lentil; chickpea; pinto.<br>Seeds (small): sesame; flax; sunflower; poppy; pumpkin; hemp.<br>Nuts: walnuts; cashew; peanuts.<br>Grains: wheat (durum, spelt, kamut); millet; oat; rye; rice; barley.<br>Sweet fruits: peaches; strawberries; mangos.<br>Vegetables: most vegetables; unpeeled sweet potatoes and mushrooms. |
| Food with medium GI ranges (56–69) | Table sugar; regular ice cream; cranberry juice; grape juice.<br>Enriched whole wheat; basmati rice; unpeeled potatoes; peeled sweet potatoes; pita bread.<br>Raisins; prunes; pumpernickel bread. |
| Food with high GI ranges (70 and above) | Sugars: glucose: dextrose; grape sugar; high fructose corn syrup; maltose; maltodextrins.<br>White bread (from endosperm).<br>Most white rice (from endosperm).<br>Peeled potatoes<br>Extruded breakfast cereals; corn flakes. |

Based on [10][11][12][13].

## 2. Obesity

Obesity is closely related to IR [14]. A body mass index over 30 is accepted as obesity. Obesity is a consequence of IR [11]; it deteriorates diabetes and makes management more difficult. One thing that should be mentioned here is that individuals with greater waist/hip ratios are also at risk of developing diabetes [2]. Obesity and derangement in lipid metabolism play a key role in the pathogenesis and development of insulin resistance, and subsequently T2D, in such individuals. Obese individuals have an increased mass of adipose tissue, which leads to lipid overflow, which in turn causes subtle inflammation via disturbed cytokines' and adipokines' secretion [15].

The key to impeding obesity is regular physical exercise and consumption of foodstuff that causes the lowest possible glycemic load (GL). This parameter is closely related to the glycemic index [13]. Glycemic load estimates the value of hyperglycemia that can ensue postprandial levels with the consumption of different types of foodstuff. Each unit of this parameter is equivalent to one gram of glucose [16]. To indicate and discuss all risk factors that are considered potential to predisposing obesity falls outside the scope of this work.

## 3. Gestational Diabetes

This is also considered as a variant of IR in that it involves the combination of the relative inadequacy of the amount of insulin being secreted and the responsiveness of different tissues of pregnant women to this hormone. The condition may disappear after parturition [17]. Obstetricians, therefore, recommend that pregnant women check their blood glucose level starting at around weeks 24–28 of pregnancy (as a part of the antenatal workout). If present, the condition is usually diagnosed in the second to third trimester, being attributed to the hormones that antagonize insulin action [18]. The majority of these cases subside after delivery, but unfortunately, some of these women will suffer from T2D or other forms of glucose intolerance after successive deliveries [17]. Solid statistics document that 70% of women with gestational diabetes

are at a high risk of developing diabetes (mainly T2D) later in their lives [19][20]. Therefore, antenatal care should not be neglected among pregnant women, especially in societies of the developing world where physical activity is almost non-existent among women in such populations. One point that must be mentioned here is that there exist special body exercises designed for pregnant women as antenatal care measures in different parts of the prosperous world. There are different pieces of evidence that suggest a link between vitamin D deficiency and gestational diabetes [21][22]. The broad lines of management in such cases include dietary changes and regular blood glucose monitoring, and certain cases may also need insulin therapy [23].

## 4. Human Insulin in Brief

Human insulin is a peptide hormone (protein) synthesized by the beta cells of Langerhans islets of the pancreas. It consists of two chains (A and B), cross-linked by disulfide bonds between cysteine residues in the corresponding chains and within the same chain, which give this peptide hormone stability, despite it being a small polypeptide of 51 amino acids. It is an anabolic hormone; to be more precise, it is the main anabolic hormone of the human body [24]. This hormone regulates the metabolism of all fuel material in the human diet, that is, carbohydrates, fats, and proteins. It does so by increasing glucose absorption from the circulation, mainly postprandially, into the hepatocytes, lipocytes, and skeletal myocytes for further metabolism [25]. High insulin levels in the blood inhibit glucose secretion from the liver into the blood circulation. The circulating insulin also promotes the synthesis of macromolecules of cellular components such as proteins in cells of different tissues of the human body and lipogenesis in adipocytes—a sort of anabolic effect of this hormone. The reverse situation is encountered when the level of circulating insulin is low, that is, the catabolic process is promoted, especially when the cells start to consume the reserve pools of fat they contain to start with. This physiological process is attributed to the sensitivity of beta cells to blood glucose levels. Insulin secretion increases as a response to a high blood glucose level, and the opposite is true in cases of hypoglycemia. The blood glucose levels indeed lie within physiological limits (4.0 to 5.9 mmol/L preprandial and less than 7.8 mmol/L postprandial, 2 h after a meal). This balance is regulated by the interplay of insulin and glucagon (an alpha pancreatic cell released hormone). Glucagon stimulates glycogenolysis and gluconeogenesis in the liver. The secretion of these two hormones into the circulation is the most pivotal biochemical mechanism to induce glucose homeostasis [26]. Serum insulin levels are measured either in international units (μIU/mL) or as molar concentration (pmol/L) (where 1 μIU/mL is 6.945 pmol/L) [27]. The typical insulin level in the blood between meals is about 8–11 μIU/mL (57–79 pmol/L) [28]. Postprandial insulin release by the pancreas actually comes in bouts, i.e., it is not linear, but rather oscillates up and down. It is believed that this regular fluctuation is necessary to extract insulin from the blood for degradation, which is vital for the down-regulation of insulin receptors in different target cells [29].

## 5. Glucose Transporters

Glucose transporters (GLUTs) are a broad group of intramembrane proteins that facilitate the transport of glucose across the cell membrane. These transporters function as uniporters because, in a concentration-dependent manner, they permit diffusion of glucose into the cytoplasm for different catabolic and/or biosynthetic purposes. The human genome encodes 14 different types of these transporters. They are uniporters because they facilitate the diffusion of a single species of a certain molecule (glucose in this case) at a time, along its concentration gradient. This is a passive process in that there is no need for ATP hydrolysis. They are categorized into three main classes, I, II, and III. Class I includes the following subgroups: GLUT1, GLUT2, GLUT3, GLUT4, and GLUT14 [30], which are the most significant and well characterized of these according to Bell et al. [31]. GLUT1 and GLUT3 are the main transporters of glucose into pancreatic beta cells. These membrane proteins, hand-in-hand with sodium-glucose transporters (SGLTs), facilitate this biological task so that insulin in appropriate amounts is released from these cells into the circulation to reach the target organs [32].

### 5.1. GLUT1

GLUT1 is a uniporter membrane protein that facilitates the transport of glucose molecules across the plasma membrane of human cells [33][34]. It expressed mostly in erythrocytes and endothelial cells (of the blood–brain barrier). It is responsible for basal glucose uptake that is sufficient to maintain cellular respiration (electron transport chain) in all cells. This transporter subtype is also widely found in fetal tissues. Expression of GLUT1 increases as intracellular glucose levels fall, and vice versa. The expression is upregulated in neoplastic cells of many tumor types, and this is sustained as such cells need huge amounts of glucose for anaerobic glycolysis (Embden–Meyerhof–Parnas pathway) to maintain the uncontrolled growth of tumors, especially in their deeper zones, as cells in such zones almost completely rely on the anaerobic variant of glycolysis.

### 5.2. GLUT2

This protein has a bidirectional glucose transport function in that it allows glucose influx and efflux across the cell membrane. It is the major glucose transfer gate between the liver and blood [35]. In addition to hepatocytes, its expression predominates widely in renal tubular tissue [36], the small intestine [37], and the beta cells of pancreatic islets. Such bidirectional glucose transport also exists in the basolateral small intestinal enterocytes. This phenomenon is vital for hepatocytes for both glycolysis and glycogenesis, as well as for gluconeogenesis and the release of glucose into the circulation. The level of the circulating free glucose per se is a prerequisite for the beta pancreatic cells to gauge and control glucose levels of the body in a homeostatic balance. The main characteristic of this protein is that all three fuel monosaccharides—glucose, galactose, and fructose—are transported through these from enterocytes into the portal circulation to reach the liver. Because it has a bidirectional action, GLUT2 is a low-affinity transporter subclass; it transports glucose across the membrane from areas of high concentration to areas of lower concentration.

### 5.3. GLUT3

GLUT3 is a high-affinity subclass; it allows glucose transport to occur in all cases, even when glucose levels are intracellularly low—a phenomenon required for neurons [38], placenta, and fetal cells [39]. This transporter protein has a significantly greater transport capacity than GLUT1 and GLUT4, as well as a higher glucose affinity than other subclasses, namely, GLUT1, GLUT2, and GLUT4 [40].

### 5.4. GLUT4

GLUT4 abbreviates glucose transporter protein type 4; it is also known as solute carrier family 2 facilitated glucose transporter member 4. In humans, it is encoded by the gene *SLC2A4* located in chromosome 17. The significance of this transporter protein was demonstrated by James et al. in 1988 and its action is regulated by insulin [41]. This protein has a significant responsibility in glucose storage; it is expressed mainly in adipocytes and striated myocytes, especially skeletal muscles [42]. Like all other GLUT subclasses, the N (amine) and C (carboxyl) ends of GLUT4 are exposed to the cytoplasm and it has 12 transmembrane alpha segments. It is believed that the primary sequence of amino acids in this protein class is what enables them to transport glucose across the cellular biomembranes in which they are studded [43]. The protein also contains the UBX-domain, where ubiquitin can tether to GLUT4 such that the protein can be sequestrated into vesicles in the absence of insulin [44]. GLUT4, when located at the cell surface, by a facilitated diffusion, permits the entry into the circulation of glucose molecules down its concentration gradient into skeletal myocytes and adipocytes. Once glucose is internalized, it is trapped by the process of phosphorylation by glucokinase (liver) and hexokinase; in other tissues, it is trapped by glucose-6-phosphate to enter the glycolytic cycle; or it is polymerized into glycogen depending on the cell type in which glucose molecules diffuse.

### 5.5. GLUT14

GLUT14 has a similar function to GLUT3, but is expressed mainly in the testis [45].

## 6. Insulin as a First Messenger in Signal Transduction Cascade

Insulin receptors exist in cell membranes. The receptor protein is a homodimer of α and β subunits. Similar to other membrane receptor proteins, the insulin receptor has polarity, the α-subunits are extracellular, and the β-subunits are intracellular; see **Figure 1**. The hormone insulin, as a first messenger, triggers a cascade of reactions when it attaches to the α-subunit of the receptor. The β-subunit is then activated. The β-subunits of the receptor display tyrosine kinase enzyme activity; therefore, a sort of auto-phosphorylation occurs in this subunit of the protein. The consequence of this initial activation is the further phosphorylation of insulin receptor substrates; the one demonstrated in diagram 2 is IRS-1. This phosphorylation process in turn activates a cascade that results in the activation of other kinases and transcription factors that mediate the intracellular effects of insulin [46]. The consequence of this is the expression and insertion of GLUT4 receptor subtypes into the membranes of myocytes and lipocytes, as well as the biosynthesis of glycogen in the liver and skeletal muscle tissues. This biosynthetic process also converts glucose residues into fat (triglycerides) in the liver, adipose tissues, and lactating tissues of mammary glands. Indeed, all of these metabolic processes operate via the activation of phosphoinositol 3-kinase ($PI_3K$) by insulin receptor substrate 1 (IRS-1). $PI_3K$ is a membrane-associated enzyme that catalyzes the conversion of phosphatidylinositol 4,5-bisphosphate ($PIP_2$) into phosphatidylinositol 3,4,5-triphosphate ($PIP_3$). This membrane phospholipid metabolite in turn activates another kinase known as protein kinase B (PKB), also called Akt or PKB/Akt. Once this is activated, PKB mediates the translocation of these vesicles (endosomes) that store GLUT4 in the cell membrane. These vesicles fuse with the membrane and deliver the GLUT4 proteins they contain to the cell membrane. This event increases the number of GLUT4 transporters in these membranes. PKB also

inhibits glycogen synthase kinase (GSK) by another step of phosphorylation [47]. In other words, the substrate of GSK, glycogen synthase (GS), cannot be phosphorylated and thus remains active. This active enzyme acts as a regulatory point to limit the synthesis of glycogen from glucose residues. A series of similar dephosphorylation effects of GS (glycogen synthase) indirectly control the rate of glycolysis and lead to lipogenesis (in tissues that can do so), and controls the rate of gluconeogenesis in hepatic tissue. These dephosphorylation reactions stimulate the biosynthesis of fat and glycogen from glucose. As a consequence, glycogenolysis and gluconeogenesis by the liver are inhibited. Moreover, the hydrolysis of triglycerides into free fatty acids and glycerol in the lipocytes is also inhibited [48]. In the basal state of the cell, after leaving the Golgi network, newly synthesized GLUT4 proteins are stored in the insulin-responsive storage compartment, abbreviated as IRC [49]. The signal initiated by the binding of insulin to its receptor ends (briefly demonstrated in **Figure 1**) by the endocytosis and degradation of these two bound proteins (insulin and its receptor) [50]. The two main sites for this clearance are the liver and the kidneys. In hepatic tissue, the clearance occurs during the first passage through the liver and the kidneys clear insulin from the systemic circulation. The half-life of insulin from being released from the beta pancreatic cell up to degradation is about 4–6 min [51].

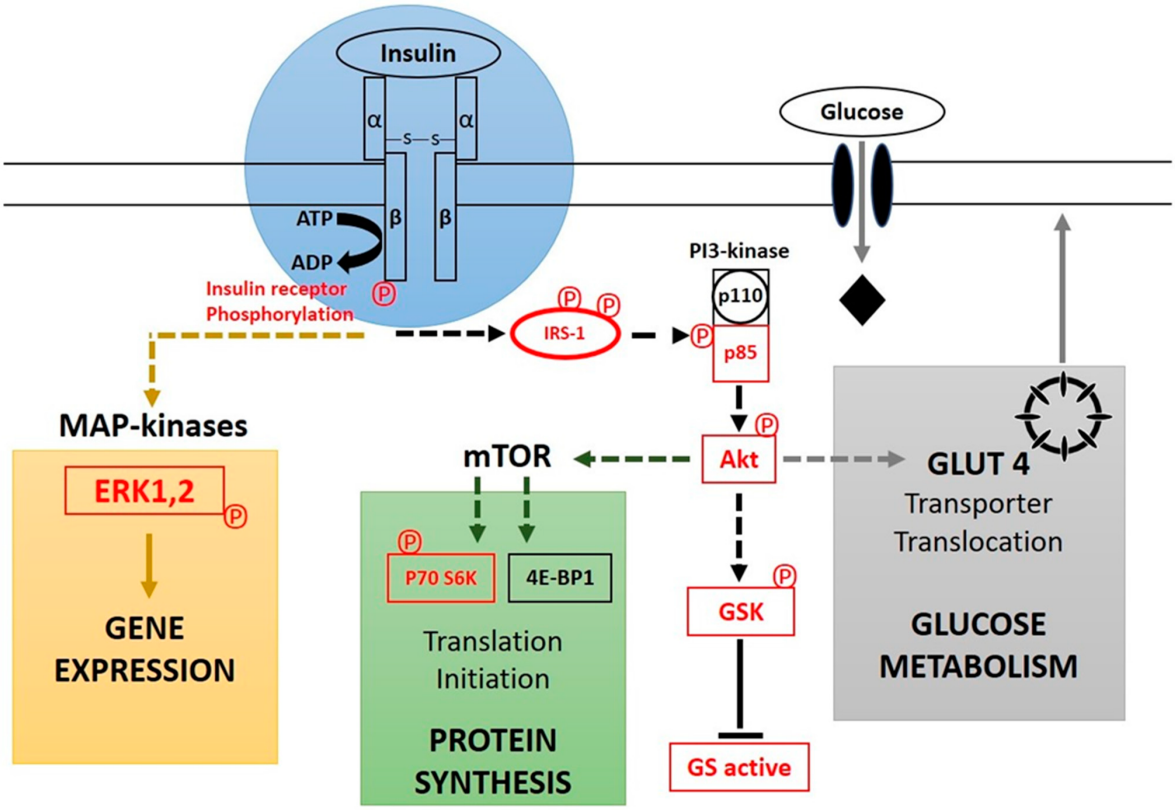


**Figure 1.** Insulin signal transduction. The insulin receptor (IR) is in blue, the MAP-kinase pathway to gene expression is highlighted in light-brown, and dark-green lines point to the proximal common pathway to protein synthesis (highlighted in green) and glucose metabolism (highlighted in gray). Phosphorylated proteins, IR (insulin receptor), extracellular signal-regulated kinases 1 and 2 (ERK1,2), insulin receptor substrate 1 (IRS-1), the p85 subunit of phosphatidylinositol 3-kinase (PI 3-kinase), Akt protein kinase (Akt), S6 protein kinase (p70 S6K), glycogen synthase kinase (GSK), and glycogen synthase (GS), are in red. P (phosphate group), (–S–S–) disulfide bond, mTOR (mammalian target of rapamycin), ATP (adenosine triphosphate), ADP (adenosine diphosphate) and MAP (mitogen-activated protein).

## 7. Physiological Effects of Insulin

The main effects are demonstrated in **Table 2** [52][53][54][55][56][57][58][59]. Individuals with poorly controlled diabetes and undetected diabetes cases can encounter cognition problems attributed to cerebrovascular incompliance. In the brain, insulin enhances learning and verbal memory [60]. Cerebral insulin enhances thermo and glucoregulatory responses to food intake; this phenomenon points to the fact that cerebral insulin coordinates a wide spectrum of homeostatic processes in our body [61]. Further, insulin favors fertility through its impact on the hypothalamus via its effect on the secretion of gonadotropin-releasing hormone [62]. Glucose is the primary fuel oxidized by neurons (in non-starving states) to biosynthesize adenosine triphosphate (ATP) to ensure the continuance of the wide spectrum of neurons' metabolic machinery. Further, it is the only fuel molecule relied on by human RBCs to synthesize ATP [63]. Insulin is needed to drive glucose molecules into the cytosol of cells to synthesize ATP. ATP (the energy currency of biological systems) is necessary for different phosphorylation processes that usually activate kinase types of enzymes or keep certain proteins inactive, which is mentioned elsewhere in this work. The Embden–Meyerhof–Parnas glycolytic pathway (an anaerobic

metabolic process) yields two ATP molecules for each glucose molecule. This process also produces a substrate (pyruvate molecule) that enters the mitochondria to produce far more ATP in an aerobic process through the Szent–Györgyi–Krebs cycle in cooperation with the electron transport chain.

**Table 2.** Direct and indirect metabolic effects of insulin.

| Parameter | Physiological Function | Improper Function/Decrease in Insulin |
|---|---|---|
| Glucose | Stimulates glucose uptake via insertion of GLUT4 in the membranes of myocytes and lipocytes. | Increase in blood glucose concentration. |
| Triglycerols (fat) | Increases lipogenesis by forcing lipocytes to take in glucose. | Decrease in lipogenesis and hyperglycemia. |
| Fatty acids | Increased esterification to triglycerides (neutral lipids). | Lipolysis of triglycerides to fatty acids and glycerol. |
| Lipolysis | Decreases lipolysis and decreases free fatty acid and glycerol in the circulation. | Hyperlipidemia |
| Glycogen | Induces glycogen synthesis, by activation of the hexokinase that activates glucose by adding a phosphate, a process that traps glucose inside the cell.<br>Inhibits glucose-6-phosphatase, which dephosphorylates glucose.<br>Activates both phosphofructokinase and glycogen synthase, which are responsible for glycogen synthesis. | Inhibits glycogen synthesis by reverse steps that induce glycogen synthesis. |
| Gluconeogenesis and glycogenolysis | Decreases these two processes by decreasing glucose synthesis from noncarbohydrate biomolecules mainly in the liver. | Gluconeogenesis in the liver from diverse substrate biomolecules. |
| Protein | Decreases protein breakdown | Proteolysis is eased, as is the case in advanced cases of diabetes. |
| Autophagy | Deceleration of degradation of damaged organelles. | Autophagy is accelerated. |
| Arterial muscle tone | Increases this, especially arterioles and micro-arteries, and thus increases blood flow. | Reduces blood flow in these by allowing muscles to contract. |
| Gastric chlorhydria | Increases hydrochloric acid secretion by the gastric parietal cells. | T he occurrence of the reverse process is expected. |
| Potassium uptake | Forces glycogen-synthesizing cells to absorb potassium with water from the extracellular fluids via translocation of the $Na^+/K^+$-ATPase to the membranes of skeletal myocytes. | Inhibits potassium absorption. |

| Parameter | Physiological Function | Improper Function/Decrease in Insulin |
| --- | --- | --- |
| Renal sodium excretion | Decreases excretion of renal sodium. | The reverse process occurs. |

Based on [52][53][54][55][56][57][58][59], GLUT4: glucose transporter type 4, Na+/K+-ATPase: ATP dependent sodium/potassium pump.

## 8. Treatment

In the early stages of IR, it is possible to hamper/stop the progression of the pathology. Oral hypoglycemic agents are the mainstay of therapeutic treatment in IR. These agents generally exert their actions via three main means: (1) increase the amount of insulin released by the pancreas, (2) increase the sensitivity of insulin receptors in different target organs in such a way that they harmonize optimally with GLUTs, (3) decrease the rate of glucose being absorbed from the intestine, and (4) help the body dispose of excess glucose through urination. Among these agents, metformin (Glucophage) is usually the first-line drug. It is prescribed at the initial stage of diagnosis, in addition to bodily exercise and weight loss strategies that patients are usually advised to perform. These agents also have their drawbacks, such as lactic acidosis; the safest among them is probably metformin [64]. Metformin decreases both gluconeogenesis and glucose absorption via the gastrointestinal tract; moreover, it increases the body's sensitivity to insulin [65]. The details of these agents fall outside the scope of this entry and thus will not be discussed.

In addition to oral hypoglycemic drugs, recent research has shown that IR can also be combatted by methods that control the amount of insulin needed by the body both by production de novo or when therapeutically taken by injection via insulin pumps [66][67]. A reduction in IR can be achieved by following low-carbohydrate and ketogenic diets. Individuals with IR are advised to consume fiber-containing food with a low amount of calories. The aim is to treat the obesity in these individuals if they should be so affected [68]. It is believed that fruit with high amounts of protein and fibers that also have low levels of calories should be recommended for this population, as these also contain antioxidants such as vitamins C, A, and E [69]. Many types of fruit such as avocado and bananas also contain considerable amounts of potassium, which is a necessary contributor to the control of blood pressure (hypertension). Many diabetic individuals also suffer from hypertension as a prominent milestone in the spectrum of metabolic syndrome. Daily exercise (bodily motion) is a preventive measure and an essential pillar of treatment to fight obesity and thus, indirectly, IR.

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