Nutrition in Metabolic Syndrome

Module 24.2

Insulin resistance: from pathophysiology to clinical assessment

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Learning Objectives:

- Understand interactions between obesity, insulin resistance and metabolic syndrome;
- Understand the role of nutrients in the onset and modulation of insulin resistance;
- Understand the clinical impact of insulin resistance;
- Describe methods to measure insulin resistance in humans.

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Key messages:

- Insulin resistance can be defined as a lower than normally expected insulin effect on glucose metabolism and/or plasma concentration at a given insulin level;
- Causes of insulin resistance are complex: altered adipose tissue endocrine functions, altered lipid metabolism also in non-adipose tissues, inflammation, and oxidative stress are emerging as the key players. Important roles are also attributable to altered nutrient sensing in the gut and CNS;
- Insulin resistance is a very common alteration with profound implications for human disease, particularly in terms of metabolic and cardiovascular morbidity. Insulin resistance is a major underlying factor in the metabolic syndrome;
- Measurement of insulin resistance with reliable surrogates provides an important tool for effective management of metabolic and cardiovascular risk in metabolic syndrome patients.
1. Obesity, insulin resistance and metabolic syndrome

The ongoing, worldwide obesity epidemic is a major threat to patients and healthcare systems because of its related morbidity and costs (1). A major obesity-related burden is related to its metabolic and cardiovascular complications, with major roles for insulin resistance, type 2 diabetes and atherosclerosis at coronary, carotid and peripheral levels. High prevalence of metabolic and cardiovascular complications does not imply that they are inevitable consequences of fat gain, and a sizable fraction of obese individuals remains metabolically healthy long after the onset of obesity (2). Identifying obese individuals at risk for life-threatening complications is a major clinical and epidemiological goal, since it would theoretically allow treatment and resources to be focused on patients who would be likely to benefit the most.

Metabolic syndrome is a cluster of cardiovascular risk factors that occur simultaneously in the same individual (3). The clinical features that define metabolic syndrome may vary slightly by different classifications, but a strong consensus has built on the role of abdominal obesity and altered glucose metabolism, reflecting insulin resistance, as major pathogenic factors (3).

Understanding the causes, consequences and clinical markers of insulin resistance in metabolic syndrome patients is the object of this module.

2. Insulin resistance definition

Insulin is a key modulator of intermediate metabolism, involved in the regulation of a variety of fundamental cell and tissue functions. Important metabolic effects of insulin occur in the post-prandial state, when variable increments of plasma insulin concentration play a major role in nutrient utilization. Under these conditions, plasma glucose elevation elicits insulin secretion leading to 1) stimulation of glucose uptake and utilization by insulin-sensitive skeletal muscle and adipose tissue; 2) inhibition of the glucose production from gluconeogenesis and glycogenolysis in the liver. Major metabolic effects of insulin however also include maintenance of skeletal muscle mass by inhibition of protein breakdown and stimulation of synthesis of selected protein fractions (4,5), as well as stimulation of lipid deposition in adipose tissue (6). In addition, important insulin effects on endothelial function (7), regulation of cell cycle, redox state (8,9) and several other pathways have been clearly described.

Insulin resistance can be defined as the inability of insulin to exert its biological effects in target tissues. It should however be kept in mind that the common clinical definition of insulin resistance refers to inadequate effects of insulin on glucose metabolism. In this context, insulin resistance may be defined as a lower than normally expected insulin effect on glucose metabolism or its plasma concentration at a given insulin level. It is also important to consider that insulin resistance may occur in the same individual for glucose metabolism but not, or to a lesser extent, for other important insulin effects. As an example, the insulin sensitivity of muscle protein turnover or adipocyte lipolysis in obese patients, who may be insulin resistant for glucose metabolism, is still under debate (6,10).

3. Insulin resistance in obesity

Obesity is a major risk factor for insulin resistance. Although not all obese individuals develop insulin resistance and its consequences, most insulin resistant patients are overweight or obese. Understanding the causes of this strong association is an important clinical goal. A major contribution of adipose tissue and altered lipid metabolism in orchestrating obesity-associated metabolic changes has been identified. An important role for oxidative stress and chronic inflammation has been also defined. In addition, new players in the regulation of insulin sensitivity have emerged with involvement of the gut and the central nervous system (CNS). These alterations will be outlined in the following section.

3.1 Adipose tissue and altered lipid metabolism

Adipose tissue – The traditional view of adipose tissue as an inert reservoir for passive fat storage has long been modified by the demonstration that adipocytes secrete a variety of
hormones (adipocytokines or adipokines) involved in the regulation of intermediate metabolism, energy metabolism, inflammation, haemostasis (11,12). Among many secreted proteins, adiponectin, a 30-kDa adipocytokine, is uniquely associated with high insulin sensitivity and reduced cardiovascular risk (11,12). Adiponectin has also been reported to increase lean tissue, and particularly skeletal muscle lipid oxidation and mitochondrial function (13). This effect appears to be mediated by activation of the master metabolic regulator AMP-activated protein kinase (AMPK) (13,14). TNF-alpha and IL-6 are, on the other hand, known activators of the systemic inflammatory response that are also secreted by adipose tissue and related to low insulin sensitivity (15).

Opposite changes in plasma adipocytokine patterns are observed in obesity and following caloric restriction (15,16) (Fig. 1). The unfavourable obesity-related pattern of low adiponectin with parallel increment of proinflammatory cytokines including TNF-alpha is strongly associated with insulin resistance, and it can be at least in part reversed by calorie restriction and loss of body fat (15, 16).

![Fig. 1. Altered patterns of adipokine secretion in obese adipose tissue may contribute to systemic and skeletal muscle inflammation, as well as to insulin resistance.](image)

The mechanisms underlying these nutrition-driven changes are not completely clear, but important roles have been proposed for oxidative stress and adipose tissue plasticity. **Oxidative stress** - *In vivo and in vitro* evidence has indeed linked excess production of reactive oxygen species resulting in oxidative stress, to metabolically unfavourable patterns of adipocytokine expression and production (19). An elegant study demonstrated that plasma lipid peroxidation markers (TBARS) are associated negatively with circulating adiponectin and positively with BMI (19). Importantly, induction of oxidative stress in cultured adipocytes lowered adiponectin expression and increased the expression of IL-6, and these changes were reversible upon antioxidant supplementation (19).

**Adipose tissue expandability** – Excess energy intake and excess circulating lipids are largely stored in adipose tissue, and increased adipose tissue mass indeed by definition characterizes obesity. Increments in adipose tissue mass may occur through an increase in cell size or in cell number. Recent evidence suggests that the inability to stimulate adipogenesis and adipocyte number may result in enlarged adipocytes, cell damage and apoptosis (20,21). The latter process may lead to unfavourable adipokine secretion profiles and it directly activates proinflammatory reactions from tissue macrophages, with enhanced production of TNF-alpha and other pro-inflammatory adipocytokines (22).

**Lipid metabolism in non-adipose tissues** - **Fatty Acids and CERAMIDE** – Obesity and excess adipose tissue are commonly associated with elevation of plasma free fatty acids (23-25). Both excess fatty acid release and lower fatty acid uptake may be observed in adipose tissue in obesity and these alterations are likely responsible for the above association (25). High plasma concentrations of fatty acids are *per se* strongly and causally associated with insulin resistance in humans, since fatty acid infusion induces insulin resistance of glucose metabolism (24-28). Despite the importance of this observation, the mechanisms underlying the negative effects of fatty acids on insulin action remain only partly understood, and complex metabolic pathways and mechanisms are involved (29). Proposed direct mechanisms involve induction of inflammation and oxidative stress, that will be discussed below in more detail, as well as endoplasmic reticulum stress (25,30). Besides their reported effect on ROS production and inflammation, excess fat substrates may accumulate in non-adipose cells and tissues including

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skeletal muscle and liver, and these alterations appear to have a direct negative impact on insulin action. Muscle and liver triglyceride accumulation has been initially investigated, and strong associations have been described between intracellular triglycerides and insulin resistance (31). Liver fat accumulation or Non-Alcoholic Fatty Liver Disease (NAFLD) may progress to non-alcoholic steato-hepatitis (NASH), cirrhosis and cancer, and liver triglyceride accumulation may represent an independent risk factor for metabolic and cardiovascular complications (32,33). Studies in skeletal muscle also indicated that intermediate products of fatty acid-triglyceride such as diacyl-glycerol may be responsible for vicious cycles leading to enhanced insulin resistance (29). More recent studies opened new perspectives in our understanding of the interactions between tissue lipid content and insulin action, by showing an important role for fatty acid channelling towards sphingolipid synthesis and ceramide excess (34). Convincing evidence indicates that the above metabolic pathway may be exceedingly activated in the presence of saturated fatty acids and inflammation, both observed in obesity (34). Ceramides have been in turn demonstrated to induce several negative changes in insulin signalling, mainly at the AKT level, with resulting inhibition of key steps of glucose uptake and utilization (34) (Fig. 2).

Fig. 2. Ceramide synthesis from serine and fatty acid is enhanced by inflammation and may lower insulin sensitivity.

Mitochondrial dysfunction - An association between obesity, insulin resistance and skeletal muscle mitochondrial dysfunction has emerged in the last decade (35). This association is notably less clear in the liver, where enhanced energy metabolism gene expression has been reported in some studies in obese insulin resistant patients (36,37). Muscle biopsy studies in Caucasian obese, insulin resistant or type 2 diabetic patients indeed demonstrated abnormalities of muscle mitochondria, and impaired mitochondrial oxidative capacity was often associated with tissue triglyceride accumulation (31,35). Reduced expression of regulators of muscle mitochondrial biogenesis such as PGC-1alpha have also been reported along with functional abnormalities in first degree relatives and offspring of insulin resistant, diabetic individuals (38).

A potential underlying cause-effect relationship has been hypothesized, with low mitochondrial lipid oxidation favouring muscle lipid accumulation and insulin resistance (35). This hypothesis is appealing but it has been seriously challenged by diverging changes in mitochondrial function and insulin action in several studies under acute and chronic experimental conditions (39-43). A breakthrough in the understanding of the association between muscle mitochondrial dysfunction and insulin resistance came with the demonstration of a stimulatory effect of insulin on muscle mitochondrial gene expression, protein synthesis and ATP production in healthy humans (5). The above report introduced the concept that the association between muscle mitochondrial dysfunction and insulin resistance could be bidirectional, and insulin resistance could primarily contribute to impair mitochondrial function in insulin resistant individuals. The onset of mitochondrial dysfunction could nonetheless cause a metabolic vicious cycle with impaired lipid utilization and worsened insulin resistance, so that improvement of mitochondrial lipid oxidative capacity remains a potential target for insulin-sensitizing therapeutic strategies (Fig. 3). Finally, it must be pointed out that oxidative stress and
inflammation are reported to cause both insulin resistance and mitochondrial dysfunction, and it is therefore well possible that their association in skeletal muscle reflects a common pro-oxidant and pro-inflammatory metabolic milieu.

**Fig. 3.** Mitochondrial dysfunction, particularly in skeletal muscle, may be favored by insulin resistance and cause additional lowering of insulin signaling.

### 3.2. Inflammation and oxidative stress

Both local and systemic inflammation may result from an imbalance in the production of pro-inflammatory and anti-inflammatory cytokines. While acute inflammation at both local and systemic levels may represent an adaptive mechanism contributing to the limitation of a specific infectious or traumatic insult, sustained activation of systemic inflammatory responses has a negative metabolic impact (44). In particular, pro-inflammatory cytokines, including TNF-alpha, activate the IKK-NFkB pathway that results in inactivation of IRS-1, and insulin signalling blockade (Figure 4). Anti-inflammatory drugs such as acetylsalicylate are, conversely, reported to prevent insulin resistance in rodent models of obesity (45,46) (Fig. 4).

**Fig. 4.** a) Pro-inflammatory cytokines impair insulin signalling by activating IKK, resulting in inactivating phosphorylation of Insulin Receptor Substrate-1 (IRS-1) and downstream activation and nuclear translocation of NFkB; b) Anti-inflammatory agents such as acetylsalicylate (ASA) rescue insulin signalling by preventing IKK-NFkB activation. Adapted from Ref 45
Production of reactive oxygen species (ROS) from incompletely reduced oxygen molecules is inevitably associated with oxidative substrate metabolism (8). Antioxidant defence systems eliminate excess ROS and maintain their concentrations within the physiological range; that indeed plays an important role in maintenance of cell and tissue homeostasis. Excess ROS production may however overcome antioxidant capacity, thereby leading to oxidative damage to tissue and disease. Importantly, oxidative stress is reported to be involved in the onset of insulin resistance in experimental models of obesity (47). Amplification of pro-inflammatory changes in peripheral tissues through enhanced proinflammatory cytokine production and activation of NF-kB nuclear translocation (48,49) is one potential mechanism involved (Fig. 5).

Fig. 5. Oxidative stress may enhance tissue inflammation through NF-kB activation and stimulation of proinflammatory cytokine gene expression

Obesity is often associated with elevation of clinical markers of inflammation such as plasma C-reactive protein or pro-inflammatory cytokines (50-52). Oxidative stress markers have been also reported to be elevated in obese individuals (17,53), and both alterations are commonly associated with insulin resistance in obese patients (50-53). As discussed above, altered adipose tissue hormone production occurs in obesity; this can be favoured by oxidative stress, and may directly favour the onset of chronic low-grade systemic inflammation by altering the balance between pro- and anti-inflammatory adipokines. In addition, negative modifications in diet and physical activity most likely contribute directly to inflammation and oxidative stress in the obese population.

Nutrients and diet – High-calorie, high-fat diets are reported to promote the onset of inflammation and oxidative stress (54-56), although these changes may vary in different tissues in terms of intensity and time-course (57). Studies in vitro also indicate direct pro-inflammatory and pro-oxidant effects of fatty acids (58,59). Importantly, these effects were mostly observed in the presence of saturated fat, with palmitate commonly employed for in vitro studies (58,59) (Fig. 6). Some studies, intriguingly, have suggested differential effects by unsaturated molecules (59), and potentially protective effects of polyunsaturated fatty acids should be further investigated. One recent study however demonstrated that acute i.v. fatty acid elevation in the presence of physiological hyperinsulinaemia causes insulin resistance by inducing excess mitochondrial ROS production and by activating the pro-inflammatory IKB-NF-kB pathway (9). The high monounsaturated fatty acid content in the infusion mixture of this study indicates that deleterious metabolic effects may not be limited to saturated fatty acids in vivo (9). Most importantly, human studies are also available linking acute or chronic increase in fat availability to oxidative stress, inflammation and insulin resistance (60-62), and several reports confirm a potential protective effect of polyunsaturated n-3 fatty acids (62,63). Although the potential independent impact of glucose on inflammation and oxidative stress at systemic and tissue level has been less extensively studied, common observations in patients with diabetes mellitus and corresponding experimental models indicate pro-oxidant and inflammatory effects of hyperglycaemia, that can play a pivotal role in the onset of diabetic complications.
Fig. 6. Free Fatty Acids (FFA) may contribute to the onset of tissue and systemic insulin resistance through several different mechanisms. DAG: di-acyl glycerol.

Physical Inactivity - Acute exercise, particularly when performed in strenuous bouts, can cause elevation of oxidative stress and inflammation markers (64). Under trained conditions, these negative effects are however compensated by the stimulation of antioxidant and anti-inflammatory pathways, and the net effects result in protection against oxidative stress and systemic and tissue inflammation with well-recognized robust health benefits (65-67). Aerobic training is also accordingly associated with improved insulin sensitivity (41,67,68). In recent years, elegant studies have also demonstrated that physical inactivity induces opposite metabolic derangements, with sustained pro-inflammatory and pro-oxidant changes as well as insulin resistance in otherwise healthy, young individuals undergoing voluntary bed-rest for periods of several weeks (69,70).

3.3. Altered nutrient sensing – role of gut and central nervous system

Increasing evidence has provided the awareness that several complex signalling networks contribute to the regulation of insulin resistance, and nutrient-sensing pathways and feedback signalling mechanisms involving the gut and central nervous system (CNS) have been extensively studied in the last decade. Importantly, gut hormones involved in nutrient sensing have emerged with pleiotropic effects on appetite, insulin secretion and substrate utilization. Glucagon-Like Peptide 1 (GLP1) is one clinically relevant example (Fig. 7), whose negative effects on appetite and positive effects on insulin secretion and activity may be impaired in insulin-resistant type 2 diabetes and obesity (71). These observations have strongly supported the use of GLP1 analogues in the treatment of type 2 diabetic patients (71), with very promising results emerging. The CNS has been also extensively studied in experimental models, leading to identification of nutrient-sensing areas whose direct effects on nutrient intake and metabolism could exert potentially relevant roles in the regulation of insulin sensitivity. CNS studies remain however difficult to reproduce in humans, and further methodological developments are likely to be needed before more robust clinical data become available.
4. Clinical burden of insulin resistance

Insulin resistance is directly associated with metabolic and cardiovascular disease (72). Most importantly for this Module, insulin resistance also represents the major candidate for the role of “common soil” for the onset of the clustered metabolic abnormalities in patients with the metabolic syndrome. These associations have been well established in epidemiological studies and will be discussed below.

4.1. Insulin resistance and metabolic syndrome

Role of visceral fat - Most sets of diagnostic criteria for metabolic syndrome do not directly include insulin resistance per se (see: Module 24.1), but they commonly include elevated plasma glucose as a surrogate marker of altered glucose metabolism. Despite the close association between obesity and insulin resistance, whose causal mechanisms have been discussed above, BMI is also not directly included among diagnostic criteria for metabolic syndrome. On the other hand, elevated waist circumference, reflecting high visceral fat content, is a fundamental criterion (3). Importantly, waist circumference is a better predictor of metabolic and cardiovascular risk than BMI itself (73-75). A number of epidemiological studies has indeed strongly established the very close link between visceral fat accumulation, insulin resistance and their metabolic and cardiovascular complications (73-75). In prospective studies, increased visceral fat is an independent risk factor for coronary artery disease, stroke, and death (3, 73-75). The reasons for the above observations appear to include biologically distinct profiles of gene expression and secretion of pro-inflammatory and pro-thrombotic cytokines, including TNF-α, IL-6 and plasminogen activation inhibitor-1 (PAI-1) (76). Elevated release of free fatty acids, that directly reach the liver and impair hepatic insulin action, is also a relevant metabolic complication of visceral fat accumulation. Surgical removal of visceral fat in rodent models restored insulin sensitivity and improved metabolic and cardiovascular risk profiles, resulting in prolonged lifespan (77). Taken together, the above observations suggest a pivotal role for abdominal obesity and related metabolic alterations in the pathogenesis of metabolic syndrome, with the potential key involvement of insulin resistance. This view is fully supported by the potential pathogenic role of insulin resistance in the onset of hypertension (through impaired nitric oxide production and altered endothelium-dependent vasorelaxation) and hypetriglyceridaemia (through enhanced VLDL production), i.e. the other components of the metabolic syndrome.
4.2. Insulin resistance and type 2 diabetes

In insulin resistant patients, plasma glucose can be maintained within the normal range through enhanced beta-cell secretion (Fig. 8). Type 2 diabetes is therefore preceded by a variable but usually long period - often up to 10 years - of normal plasma glucose. The inability to enhance insulin secretion indefinitely and rather a decline in beta-cell function may then lead to pre-diabetic alterations that include Impaired Fasting Glucose (IFG: 100-125 mg/dl; 5.6-6.9 mmol/L fasting glucose) and Impaired Glucose Tolerance (IGT: 140-199 mg/dl, 7.8-11.1 mmol/L 2-hour glucose following Oral Glucose Tolerance Test). These conditions represent high risk for the development of diabetes and are collectively defined as "prediabetes". The diagnosis of type 2 diabetes finally requires fasting plasma glucose above 126 mg/dl (6.9mmol/L), 2-hour OGTT glucose above 200 mg/dl (11.1 mmol/L) or HbA1c above 6.5%. The natural history of type 2 diabetes can be accelerated by worsening of insulin resistance due to further weight gain, changes in lifestyle or intercurrent disease that may enhance insulin resistance. Importantly, people with prediabetes already have an increased risk of developing cardiovascular disease compared to metabolically healthy individuals (78).

Fig. 8. Natural history of type 2 diabetes

4.3. Insulin resistance and cardiovascular disease

There is no doubt that insulin resistance is a strong risk factor for cardiovascular disease. As discussed above and throughout this module, a cluster of separate, independent risk factors may also contribute to enhance the risk for cardiovascular events in insulin-resistant individuals. These additional factors include those combined in the metabolic syndrome, as well as low-grade systemic inflammation, elevated pro-inflammatory cytokines, pro-thrombotic alterations, and altered adipokine patterns. It is important to point out that several studies agree in suggesting that clustering of cardiovascular risk factors, as favoured by insulin resistance in the metabolic syndrome and in other high-risk conditions, synergistically enhances cardiovascular morbidity and mortality beyond expected levels from the impact of single factors (79).

5. Measurement of Insulin Resistance

Based on the above discussion, measurement of insulin resistance in vivo may provide crucial information on metabolic and cardiovascular risk in any given patient or population (80). Early detection of insulin resistance may be crucial in planning appropriate and effective prevention of progression to more advanced stages of cardiovascular risk.
Repeated measurements may also provide useful clinical markers for evaluation of treatment effectiveness in modification of risk profile. While measurement of cellular and tissue events requires tissue collection through biopsy which is not commonly feasible in humans, the assessment of insulin effectiveness in promoting tissue glucose utilization may be performed in vivo through direct or indirect surrogate methods.

A number of established tests may indeed be used to measure insulin resistance in clinical research: the choice depends on sample size and type of study to be undertaken. The euglycaemic clamp is commonly considered the ‘gold-standard’ test, but it is highly labour-intensive and is most useful for physiological studies on small numbers of subjects. A simpler approach using HOMA is more appropriate for large epidemiological studies. In clinical practice however limitations generally apply and simple tests that can be repeated over time are usually employed, based on measurements of fasting plasma glucose and insulin.

**Euglycaemic Hyperinsulinaemic Clamp:** this technique is usually considered the gold standard for measurement of insulin resistance (81). It is based on simultaneous infusions of insulin at a constant rate usually resulting in peak-physiological hyperinsulinaemia (comparable to post-prandial peak insulin levels), and of glucose at variable rates aimed at counteracting the physiological glucose-lowering effect of insulin and to maintain euglycaemia (Fig. 9). Clamp duration may vary but it is commonly two to three hours and insulin action is inferred by the amount of glucose needed to maintain euglycaemia and to prevent a fall in glucose: a higher glucose infusion rate (corrected for body weight) (GIR) reflects higher insulin sensitivity. Additional information may be inferred using constant infusions of tracers such as stable glucose isotopes, that allow the calculation of glucose turnover rates and hepatic glucose production under fasting conditions.

**Fig. 9.** The gold-standard hyperinsulinemic-euglycemic clamp technique to measure insulin sensitivity involves constant i.v. insulin infusion and variable glucose infusion to maintain basal glucose levels. The amount of glucose infused reflects insulin-mediated glucose disposal and is therefore an accurate measure of whole-body insulin sensitivity. Glucose infusion rate (GIR, mg/kg/min) may be commonly calculated in the last 30 minutes of a three-hour clamp.

The clamp technique can be considered very precise and accurate. Its results represent a reliable evaluation of peripheral insulin resistance under stimulated conditions, with a prominent role for skeletal muscle tissue. It is however labour-intensive and time-consuming and it requires experienced personnel. Its application is therefore limited to relatively small sample sizes and it may not be feasible in large epidemiological studies or in routine clinical practice. On the other hand, the clamp has commonly been used to test the reliability of, and to validate, the alternative measurements that have been proposed.

**Insulin Tolerance Test (ITT):** this technique is similar in principle to the clamp, in measuring the slope of the decline in plasma glucose concentration over 40 minutes after the bolus i.v. administration of 0.1 U/kg regular insulin. The technique is accurate but its high risk of causing hypoglycaemia is a major drawback and ITT is not employed in clinical practice, and only rarely in research.

**Oral Glucose Tolerance Test (OGTT):** this test is very commonly used in clinical practice since it is a cornerstone in the diagnosis of type 2 diabetes. Glucose, 75g, is administered orally under fasting conditions, and plasma glucose and insulin concentrations are measured at baseline and 30,60,90,120 minutes after glucose ingestion.
The results reflect both insulin sensitivity and beta cell function in insulin secretion, since changes in plasma glucose depend on both insulin sensitivity and the amount of insulin secreted in response to the glucose challenge. For clinical purposes, a plasma glucose above 140 mg/dl (>7.8 mmol/L) reflects impaired glucose tolerance, while a plasma glucose of >200 mg/dl (>11.1 mmol/L) indicates the presence of diabetes mellitus. For research purposes, several insulin resistance indexes have been proposed based on OGTT results, generally using 120 minutes of glucose and insulin data, and recording the areas under curve for both (82).

**Fasting Insulin and Glucose:** Insulin resistance indexes based on fasting insulin and glucose are easiest to obtain and therefore very commonly used in clinical practice. They should be used with the following limitations in mind: 1) they reflect insulin resistance under basal, non-stimulated conditions; 2) fasting plasma insulin not only reflects insulin resistance but is also strongly dependent on insulin secretion, distribution and catabolism.

**Fasting Insulin:** elevated fasting plasma insulin strongly suggests insulin resistance. Its validity as a surrogate measure should however be questioned in patients with altered or impaired beta-cell function such as patients with insulin resistant type 2 diabetes. Plasma insulin is however useful in epidemiological studies and it may indicate elevated cardiovascular risk since it has been reported to be associated with high levels of common cardiovascular risk factors.

**Homeostasis Model Assessment (HOMA):** HOMA is based on the product of fasting glucose (mmol/l) (FG) and insulin (mU/l) (FI), divided by 22.5 as follows (83):

\[
\text{HOMA-R} = \frac{(\text{FG} \times \text{FI})}{22.5}
\]

HOMA calculators are available free at several websites, such as University of Oxford at www.dtu.ox.ac.uk/homacalculator/download.php. HOMA has been validated against the euglycaemic clamp in most available reports in adult populations, although weak or non-significant correlations have been reported in other studies (84,85). As stated above, it should be kept in mind that HOMA measurement reflects different aspects of insulin resistance from the clamp technique. Its cost-effectiveness has however made HOMA a very popular surrogate measure of insulin resistance that is widely employed in clinical research and which can be used in clinical practice.

Other surrogate measures have also estimated insulin resistance using methodology based on fasting plasma glucose and insulin, the QUICKI and FIRI tests being among the most commonly utilized (86).

**Mathematical modelling approach:** more sophisticated modelling approaches have been sought by increasing the number of measurements following i.v. glucose bolus infusion, with or without insulin sampling. These models have yielded important insights towards our understanding of insulin resistance in human disease, but their detailed description falls beyond the scope of this review.

### 6. Summary

Insulin resistance, defined as a lower than normal insulin effect on glucose metabolism or concentration at a given insulin concentration, is a very common alteration with profound implications for human disease. Causes of insulin resistance are complex, and recent views indicate a major involvement of inflammation and excess visceral adiposity with altered lipid deposition in non-adipose tissues. Insulin resistance is at the core of the metabolic syndrome, being associated with plausible causal roles in all of its components. Measurement of insulin resistance is relatively easy and informative when surrogate measures are employed with a full awareness of their limitations. Insulin resistance measurements may provide important tools for management of metabolic and cardiovascular risk in metabolic syndrome patients and in the insulin-resistant population at large.
7. References

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