ECRONICON OPEN ACCESS

EC NUTRITION
Review Article

Insulin Resistance in Primary Dietary Care Practice. Review of the Evidence and a Proposal for Daily Use

Elisabeth Govers[1,2]*, Ismay Wiggers[1,3], Harriet Verkoelen[1,4] and Dave Schweitzer[1,5]

[1]*Knowledge Centre for Dietitians on Overweight and Obesity, Amsterdam, The Netherlands*

[2]*European Federation of Associations of Dietitians, European Specialist Network of Dietitians on Obesity, Emmerich, Germany*

[3]*Primary Care Dietitian Practice Dietiek Op Maat, Bavel, The Netherlands*

[4]*Primary Care Dietitian and Diabetic Nurse Practice, Buren, The Netherlands*

[5]*Department of Endocrinology, Reinier de Graaf Hospital, Delft, The Netherlands*

***Corresponding Author:** Elisabeth Govers, Knowledge Centre for Dietitians on Overweight and Obesity, Amsterdam, The Netherlands.

Received: May 26, 2021; **Published:** June 30, 2021

Abstract

Background: Insulin resistance (IR) is a relevant metabolic problem in overweight, obesity, type 2 diabetes mellitus, cardiovascular disease, malignant disease and Alzheimer's. According to the guidelines, dietitians measure body weight, body mass index, comorbidities, and waist circumference to assess baseline characteristics and propose treatment goals to patients. Vigorous sustained insulin resistance suppression is usually overlooked. Our research focused on the importance of the determination of IR in dietary practice and to use IR as priority measure in the dietary management of patients with the metabolic syndrome and related comorbidities.

Methods: A literature review on the relevant data on insulin resistance, its related pathologies and how to treat it.

Results: We selected 100 articles on the etiology, pathology and diagnosis of IR. The pathogenesis is mainly caused by a diet rich in carbohydrates and fat combined with a sedentary lifestyle and enhanced by medication. IR lies at the basis of a large number of diseases. Several practical methods for IR quantification are summarized on which we based a composite score (the diagnostic IR score card) to be used in those patients in urgent need of a nutritional intervention. Preferably as early as possible before irreparable damage is a fact.

Conclusion: IR is one of the leading causes of metabolic disorders to be addressed in primary and nutritional care. We pledge to shift the focus on management in dietitians' practices from body weight as a clinical endpoint to deep and sustainable IR suppression. To quantify IR at baseline and to define it as an clinical endpoint, we propose a composite score for use as a measure for dietary carbohydrate restriction. Future diagnostic and diet intervention studies are needed to strengthen the evidence for tailor made carbohydrate restriction in patients with insulin resistance and metabolic syndrome.

Keywords: *Insulin Resistance; Metabolic Syndrome; HOMA-IR; Comorbidities; Waist Circumference*

Abbreviations

AAs: Amino Acids; BCAAs: Branched-Chain Amino Acids; 11beta-HSD1 and 2: 11-Beta-Hydroxysteroid Dehydrogenase; BMI: Body Mass Index; CID: Chronic Inflammatory Disease; CRP: C-Reactive Protein; CVD: Cardio Vascular Disease; DBP: Diastolic Blood Pressure; FBG: Fasting Blood Glucose; FPI: Fasting Plasma Insulin; FTG: Fasting Triglycerides; GLP-1: Glucose Like Peptide 1; HDL-C: High Density Li-

poprotein Cholesterol; HEC: Hyperinsulinemic Euglycemic Clamp; HOMA-IR: Homeostasis Model Assessment of IR; IFN-γ: Interferon-γ; ILGF-1: Insulin Like Growth Factor-1; IL-6: Interleukin 6; IL-8: Interleukin 8; IR: Insulin Resistance; LDL-C: Low Density Lipoprotein Cholesterol; LPS: Lipopolysaccharides; MCs: Mast Cells; MetS: Metabolic Syndrome; MMPs: Matrix Metalloproteinases; NAFLD: Nonalcoholic Fatty Liver Disease; PAI-1: Plasminogen Activator Inhibitor 1; PCOS: Polycystic Ovarian Syndrome; PFT: Personal Fat Threshold; QUICKY: Quantitative Insulin Sensitivity Check Index; RNS: Reactive Nitrogen Species; ROS: Reactive Oxygen Species; SBP: Systolic Blood Pressure; SCFAs: Short Chain Fatty Acids; T2DM: Type 2 Diabetes; TC: Total Cholesterol; TG: Triglycerides; TJs: Tight Junctions; TLR-4: Toll-Like Receptor 4; TNF-α: Tumor Necrosis Factor Alfa; VAT: Visceral Adipose Tissue; WAT: White Adipose Tissue; WC: Waist Circumference

Introduction

Treatment of insulin resistance (IR) is not a common part of guidelines to prevent or treat obesity or type 2 diabetes (T2DM). Health professionals are therefore insufficiently informed about the importance of IR as an underlying cause of various disorders and excess mortality. Because inadequate attention is paid to IR, there is a risk of failing prevention. This review calls for more attention to IR as a central theme in the treatment of overweight and obesity, T2DM, cardiovascular disease (CVD) and other comorbidities. To raise awareness, we looked at the evidence of IR as a major cause of disease and various health outcomes. We thereby submit some of the relevant evidence about IR as a cause of various disorders. Finally, we propose an instrument to measure IR in primary care.

During the last 30 years, much insight is gained on IR and its effects on human health [1,2]. IR has been linked to central obesity, T2DM [1], cardiovascular risk factors (age, blood pressure (SBP an DBP), total cholesterol (TC), triglycerides (TG), HDL-C, LDL-C concentration), and cardiovascular disease [3]. The general approach in treatment of obesity and its comorbidities to date is usually focused on energy intake, physical exercise, behavioral therapy, and bariatric surgery [4]. IR as the underlying cause of T2DM is well known; its cause of obesity is less accepted. The notion of existing IR as the underlying cause of other diseases, e.g. metabolic syndrome (MetS) or T2DM, or even cancer deserves far more attention. Our research question was: what is the etiology of IR, what is the relation between IR and pathology, and how can IR in primary health care be diagnosed in a simple way and be made part of the health assessment of dietitians in primary care?

Methods

This review summarizes the results of a systematic literature study looking into the etiology of IR, it's relationships with several health conditions, and methods to diagnose IR. We researched in PubMed and Google Scholar on reviews and RCTs with the search term Insulin Resistance; IR and etiology; pathology caused by IR; diagnosis and diagnostic tools of IR. 140 articles were selected, of which 100 fit the inclusion criteria.

The etiology of insulin resistance

The main clinical feature of IR is an abundance of visceral fat (VF), measurable by waist circumference (WC), caused by weight gain through consumption of high energy diets, causing low grade inflammation in white adipose tissue (WAT). Two pathways are involved: gut microbiota that are changed by a high saturated fat diet [5], and glucose and energy metabolism overreacting to an abundance of dietary carbohydrates, in combination with sedentary behavior [6]. Figure 1 shows how the gut microbiome triggers the inflammation process by the change of the balance between intestinal bacteria Firmicutes (Gram-positive) and Bacteroidetes (Gram-negative) as a result of high fat diet. By consuming a typically Western high carbohydrate, high fat, low fiber containing diet, the balance of the intestinal microbiome alters and the tight junctions (TJs) between cells become lost, the leaky gut. As a result, increased intestinal absorption of lipopolysaccharides (LPS), the major component of the outer membrane of Bacteroidetes, takes place. LPS is a strong activator of toll-like receptor-4 (TLR-4), which is expressed in many cells like macrophages [5]. The disbalance of gut microbiota caused by this process leads to insulin resistance [5]. At the same time, within the gut, short chain fatty acids - acetate, propionate, and butyrate (SCFAs) - and second-

ary bile acids become reduced, and the concentration of branched-chain amino acids (BCAAs) increases, both changing the micro-biotic intestinal balance. Lower SCFA levels also affect the TJs, contributing to increased intestinal permeability [5]. Increased BCAAs levels have shown to be associated to a five times greater risk of T2DM [7]. Moreover, diminished quantities of secondary bile acids that promote GLP-1 secretion impair insulin sensitivity. A Western diet not only induces leaky gut through LPS destruction of the TJs, but it delivers an overload of chylomicrons to carry LPS to tissues and organs [7]. A different pathway leading to the damage of TJs is formed by enterobacteria and gliadin leading to the release of zonulin, which is involved in chronic inflammatory diseases (CIDs) like Chron's disease, celiac disease and colitis, and some of the inflammatory processes leading to IR related diseases [8].

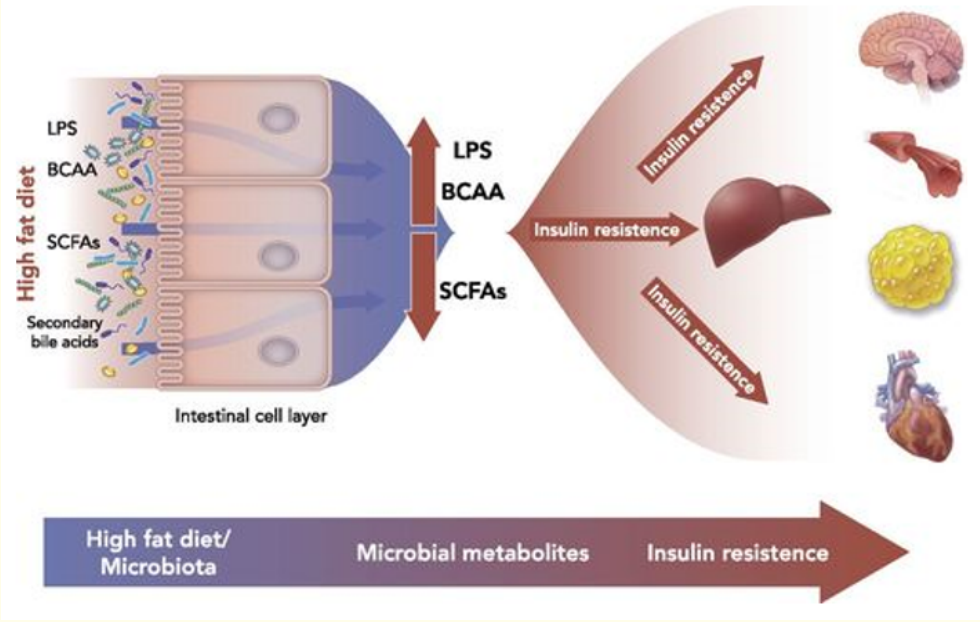

Figure 1: *High-fat-diet-induced insulin resistance.*

High-fat diet modulates the microbiota and induces an alteration in the intestinal barrier associated with an increase in absorption and circulating levels of LPS and branched-chain amino acids (BCAA) and a reduction in acetate, propionate, and butyrate (SCFA) and secondary bile acids. LPS induce subclinical inflammation, insulin resistance, and an increase in adipose mass. An increase in circulating BCAA is associated with a fivefold increased risk of developing T2DM. A decrease in SCFA affects tight-junction protein expression, contributing to increased intestinal permeability. Figure: Courtesy of MJA Saad, Dep Internal Medicine, State Un.Campinas (UNICAMP), Brazil.

Clinically, there are several effects of IR. The condition acts on brain cells by inducing chronic inflammation leading to anxiety and mood disorders [9]. It influences behavior, food choice, and healthy lifestyle, thereby stimulating the production of reactive oxygen and nitrogen species (ROS and RNS) leading to impaired synthesis of serotonin, dopamine and norepinephrine [9]. Both processes are associated with a decrease of the cerebral reward system and degenerative changes in the amygdala, the localized areas in the regulation of mood, fear, and anxiety [9].

The inflamed visceral fat is an active endocrine organ that releases a series of macrophages, pro-inflammatory cytokines, such as tumor necrosis factor alfa (TNF-α) and interleukin-6 (IL-6), but also leptin, adiponectin, plasminogen activator inhibitor 1 (PAI-1), and resistin, involved in cascades of low-grade inflammation [10]. In 1993 two studies showed the significant role of TNF-α release in insulin

resistance [11]. A number of adipokines play a role in the dynamic control of energy metabolism, like switch buttons between energy intake and expenditure through mediation by insulin. Moreover, TNF-α blocks insulin receptors in brain, adipose tissue, liver, and muscles, resulting in local (brain) insulin resistance [12]. In parallel, blood adiponectin levels - a powerful promotor of insulin-sensitivity - decrease [13]. Clinically, low adiponectin levels are associated with hypertension [14]. High TNF-α levels are also associated with inflammatory joint and inflammatory bowel diseases [15].

A special role to enhance IR and its negative consequences is played by mast cells (MCs). They originate from hematopoietic stem cells and home in the mucosa and skin. MCs, like macrophages or T-cells, are inflammatory cells. High numbers of MCs in WAT from obese subjects were found compared to lean subjects [16]. MCs release granules containing histamine, heparin, cytokines, e.g. interleukin 6 (IL-6), TNF-α, interferon-γ (IFN-γ); chemokines like interleukin-8 (IL-8); proteases (cysteinyl cathepsins and matrix metalloproteinases (MMPs)), chymases and tryptases [17]. MCs act together with macrophages in WAT [18]. MCs also release prostanoids and leukotrienes and response to IgE-medicated reactions is well known in allergic reactions but also in obesity [19,20]. Activated MCs are also found in normotensive human heart muscle in the elderly with co-existing atherosclerotic plaques and aneurysms [21]. LDL-C binds to MC proteoglycans (i.e. heparin) and activates resting macrophages to form macrophage foam cells [22,23]. Local production of heparin by MCs and hypertension are connected [24]; the same applies to T2DM, especially in diabetic retinopathy [25], although more research is needed to improve our understanding.

IR is an adaptive process leading to a reduction of insulin receptor numbers and insulin receptor substrate-1 (IRS-1) expression, an increase of IRS-1 serine phosphorylation, and attenuation of downstream signaling. Due to feedback, in the case of IR, a decrease of glucose signaling leads to hyperinsulinemia. Besides of high levels of LPS, more molecules are involved to trigger IR: saturated fatty acids and amino acids (mainly caused by the intake of methionine and the aromatic amino acids phenylalanine and tryptophane). IR is not only regulated by the IRSs but also through lipogenesis, lipid oxidation, protein synthesis and turnover, and hepatic gluconeogenesis. Moreover, the modification of proteins by metabolites and lipids, including acetylation and palmitoylation, plays a role [26]. A 2-fold odds to induce IR was shown among young males who were consuming large amounts of BCAAs, (isoleucine, leucine, valine) and aromatic AAs (phenylalanine, tyrosine) taking the HOMA-IR as a surrogate marker. In young females, similar odds were found for high leucine, valine, and phenylalanine consumption [26].

A sedentary lifestyle promotes IR. In a study among Spanish workers, most sedentary individuals had a higher BMI, greater WC, higher SBP, and a more atherogenic lipid profile. Moreover, there was a positive relationship between hours of sitting time and C-reactive protein (CRP), HOMA-IR, TG/HDL-C ratio, and fasting plasma insulin (FPI) concentration [27]. A study among Asians found that longer TV-watching time was significantly associated with higher SBP, TC, TG, CRP, HOMA-IR, and lower adiponectin [28].

Cortisol plays a contributive role in the odds of insulin resistance. Cortisol levels rise in case of chronic stress, leading to craving for food rich in fat and carbohydrates, and so, indirectly leading to weight gain and IR. Cortisol handling depends on two enzymes: 11-beta-hydroxysteroid dehydrogenase (11beta-HSD1 and 2). 11beta-HSD1 activates inactive cortisone to cortisol; 11betaHSD2 acts vice versa. High 11beta-HSD1 levels, induced by growth hormone and Insulin Like Growth Factor-1 (IGF-1) contribute to the development of IR and visceral obesity. A similar process takes place in stressful periods, leading to high cortisol levels. Corticosteroid containing medication leads to an exogenous excess of cortisol-like derivates and stimulates chronic stress. Savas., *et al*. showed that corticosteroid use was found twice as much in obese subjects versus normal weight, resp. 27.0% vs. 11.9% (both $P < .001$), 10.5% of them reporting weight gain. The largest differences between groups were found in users of inhaled corticosteroids, and in those using two or more steroid-containing formulations at the same time [29]. Female users of nasal spray were more likely to suffer from MetS than non-users, and users of inhaled spray were more likely to suffer from MetS compared to non-users: (OR: 1.20; 95% CI 1.06 to 1.36) and (OR: 1.35; 95% CI 1.24 to 1.49), resp. Chronic use of inhaled steroids was associated with higher BMI in men and women [30].

Importantly, weight gain was also associated with the chronic use of beta-blockers and other antihypertensives, antidepressants, SU-derivatives, and antipsychotics [31], thus promoting IR. However, IR development among weight gainers is variable since it depends on the type of fat distribution: each SD gain of subcutaneous WAT reduces IR risk with 48%, contrary to each SD gain of visceral adipose tissue (VAT) increases IR risk by 80% [32].

IR as the cause of pathology

Contrary to common belief, lean-looking subjects may suffer from IR [2]. The gene encoding for N-acetyltransferase 2 peptide (rs1208 "A" allele) is associated with IR and found in lean and obese humans [33]. Studies have shown higher odds of T2DM expression and several biochemical markers, i.e. FBG, HbA1c, TC and LDL-C, TG [34]. In the general population high FPI concentrations and high HOMA-IR were independently associated with an increased risk of hypertension showing women at greater risk than men [35], and in CVD [36]. In a study among women of 60 - 79 years, it was found that IR was a stronger predictor of stroke and CVD compared to insulin secretion and chronic hyperglycemia [36]. Furthermore, IR has been identified to be a strong risk factor in the etiology of several cancers: thyroid [37], endometrial [38], pancreas [39], prostate, especially in men over 65 years of age [40] and in lean sedentary men [41]; colorectal [42]; and breast cancer in postmenopausal women [43]. Cancer growth is enhanced in IR because cancer cells require insulin as a fuel to proliferate via insulin auto receptors [44]. In this aspect, IR is of great importance in patient care, as it is one of the stepping stones to disease and early mortality.

The role of IR on polycystic ovarian syndrome (PCOS) has been acknowledged widely [45] and PCOS is related to familiar T2DM [46]. Skin diseases like acanthosis nigricans, acne, and psoriasis are strongly linked to IR [47], as well as cataract [48], the latter especially in patients with T2DM. The role of IR in non-alcoholic fatty liver disease (NAFLD) [49] and in hepatitis B and C [51] and Alzheimer's' disease is widely accepted [51]. Table 1 shows several conditions that are strongly associated to IR.

Alzheimer's disease
Cancer
(Postmenopausal) Breast cancer
Colorectal
Endometrial
Pancreas
Prostate
Thyroid
Cardio vascular disease
Hypertension
Dyslipidemia: high triglycerides; high small particle LDL; low HDL; high total cholesterol
Myocardial infarction
Stroke
Impaired glucose tolerance
Diabetes type 2
Inflammatory bowel diseases
e.g. Chron's disease
Disbalance of gut microbiota
Liver disease
Non Alcoholic Fatty Liver Disease

Liver steatosis
Hepatitis B and Hepatitis C
Gall bladder disease
Mental disease
Depression
Anxiety disorder
Impaired synthesis of dopamine, serotonin and norepinephrine
PCOS
Polycystic Ovarian Syndrome
Rheumatic arthritis
Osteo arthritis
Sarcopenia
Skin disease
Acanthosis nigricans
Psoriasis
Acne

Table 1: *Diseases associated with insulin resistance.*

Diagnosis of insulin resistance

The golden standard (direct method) for diagnosing IR is the hyperinsulinemic euglycemic clamp (HEC). The amount of glucose needed to keep serum glucose constant at a certain concentration, determines IR presence, absence, or severity. However, HEC is a complicated tool used in research settings and remains unpractical in daily care. In table 2 the different methods are compared to the HEC. Pioneering work on IR has been done by Joseph Kraft, who investigated pre- and postprandial insulin concentrations in 14,000 individuals over 40 years. His data revealed a variety of insulin levels at baseline, post-meal and a range of insulin spikes after the intake of food. From the Kraft data, algorithms were adopted to predict lifetime T2DM development [52]. Later, different equations based on population data were developed to be used in epidemiological studies: HOMA-IR (homeostasis model assessment of IR), QUICKY (Quantitative insulin sensitivity check index) and McAuley. These equations are used to indirectly calculate IR:

Test	IR at P75	P90	Sensitivity%	Specificity%	Probability*
Fasting Plasma Insulin	74 pmol/l	103 pmol/l	0.57	0.81	5.3
McAuley equation	8.5	9.8	0.75	0.91	9.2
QUICKI equation	0.36	0.38	0.65	0.87	5.1
HOMA-IR	2.6	4.1	0.65	0.87	5.1
HOMA-IR in prepuberty	2.67 boys 2.22 girls		88.2 100	65.5 42.3	-
HOMA-IR in puberty	5.22 boys 3.82 girls		56 77,1	93.3 71.4	-

Table 2: *Predictors of insulin resistance based on population research and validated by HEC.*

**: Probability (Odds) of IR in case of a positive test.*

- **HOMA-IR:** Insulin (µU/m) × [glucose (mmol/l)/22.5]; normal ref. range (0.7 - 2.0); insulin resistant (> 2.0 - 2.6) [54]. HOMA-IR depends on age, race, and body weight. Kurtoğlu., *et al*. calculated a cut-off value for IR children pre-puberty being ≥ 2.6 in boys and ≥ 2.2 in girls; in puberty it is ≥ 5.2 and ≥ 3.8 respectively [53].

- **QUICKI:** $1/(\text{insulin}_0 + \log \text{glycemia in mg/dl})$, normal reference level: ≥ 0.45; insulin resistance likely: 0.30 - 0.45; diabetes likely: ≤ 0.30 [54].

- **McAuley:** Mffm/I=exp [2.63 - 0.28ln (insulin) - 0.31ln(TAG)], an equation of FPI and fasting triglycerides; normal reference range < 5.8. (Mffm = fat free mass) [55].

Insulin-based indirect IR prediction

FPI (Fasting plasma insulin): The cut-off point for IR with sufficient specificity was set at 74 pmol/l in obese adults [56]. Normal values in healthy individuals of FPI are in most cases below 10pmol/l. Kraft found 97.4 pmol/l in a heterogenous group of diabetic and non-diabetic patients [57]. In obese patients the prevalence of IR was 78% [56]. These values have been confirmed by Polonski who found significant differences in insulin secretion after meals: FPI in obese started with 175.5 +/- 18.5 pmol/l, rose to 350.5 +/- 81.9 pmol/l after lunch and at last to 373.6 +/- 64.8 pmol/l after diner, while insulin levels didn't normalize in between [58]. In table 3 the insulin values indicating IR at several moments are presented.

Lipid-based indirect IR prediction

FTG-HDL-C ratio (fasting Triglyceride-HDL ratio): In a study comparing HOMA-IR (set at 2.6) with lipid ratios, in overweight and obese men and women, and normal-weight women, significant associations were found with IR for FTG/HDL-C ratio, as well as for FTG. Optimal cut-off: FTG: ≥ 1.78 mmol/l (men); ≥ 1.49 mmol/l (women); FTG/HDL-C ratio ≥ 1.51 (men); ≥ 0.84 (women) [60].

LDL-C/HDL-C ratio: To distinguish IR this ratio is set at ≥ 3.80 (men); ≥ 3.82 (women) [60].

C reactive protein (CRP)-based indirect IR prediction

CRP (C reactive protein): A CRP level of < 1 mg/l indicates a low risk of developing CVD later in life; 1 - 3 mg/l: moderate risk; > 3 mg/l: high risk [61]. CRP is associated with HOMA-IR in obese or not obese men and women [62]. In Chinese individuals an association was found with T2DM (HOMA-IR (0.230, P < 0.001); BMI (0.305, P < 0.001) and WC (0.240, P < 0.001)) [63]. Sometimes CRP is presented as a feasible way to diagnose IR, but CRP is not fit for individual use because additional processes such as inflammation, trauma, or malignancy have influence on CRP.

Non-laboratory-based methods to calculate IR

- WC: A waist circumference of ≥ 88 cm in Caucasian females and ≥ 94 cm in males indicates IR. In Asian men ≥ 90 cm and ≥ 80 cm in women agrees with IR. In African Americans IR is set at ≥ 102 cm in men and ≥ 98 cm in women [60].

- BMI: A BMI of ≥ 25 kg/m^2 for Caucasians, and ≥ 23 kg/m^2 for Asians, combined with one or more comorbidities, e.g. hypertension, dyslipidemia or impaired glucose tolerance is a strong predictor of IR. In African Americans, a BMI of ≥ 30 kg/m^2 in men and ≥ 32 kg/m^2 in women is a strong predictor of IR [60].

- Significant weight gain, despite efforts to keep body weight stable [64,65].

- The Metabolic Syndrome (MetS) is a strong predictor of IR. There are 4 definitions of Met(S) with and without IR as part of the definition (See table 4).

- Middle upper arm circumference (MUAC). Chinese well-fed populations showed correlations with BMI, WC, waist-to-hip ratio (WHR), HOMA-IR, LDL-C, and HDL-C [66]. MUAC was independently associated with HOMA-IR (β = 0.036, P < 0.001) after adjusting for age, gender, WHR, TG, LDL-C and HDL-C. MUAC predicted central obesity (OR: 2.129, 95%CI: 1.311-3.457, P = 0.002) [67]. To our knowledge, MUAC data for IR prediction are not available for Caucasians or African Americans.

The diagnostic score card

In this review we have summarized several validated indirect IR assessments to diagnose IR and concluded that most of them are too complicated and expensive for use in primary care. This prompted us to develop a feasible, inexpensive diagnostic tool for establishing IR by dietitians running clinics in primary care. A second argument to develop a diagnostic tool is, that MetS is classified in very many ways, see table 4. When MetS is diagnosed, IR has probably been present without symptoms for a long time. We are convinced that early detection of IR can prevent patients to develop MetS or any of the other diseases mentioned in table 1.

That is the reason why we introduce and propose a diagnostic IR score card, designed in a simple way to diagnose IR in primary practice, to be applied in treatment and to be used in the follow-up of patients in dietary and lifestyle management. In the scorecard (See table 5) the criteria are: weight gain despite attempts to keep it stable; a large WC; MetS criteria (SBP or FBG); or fasting TG- HDL-C ratio, LDL-C/HDL-C ratio; and the use of weight promoting medication. Because these data are available in most patient files and referral notes, the dietitian can make a quick assessment of the presence of IR. These data can then be put in the model and each one scores one point. In case the patient scores 4 points or more it is very likely that the patient has developed IR.

	NCEP ATP III 2015	WHO 1998	EGIR 1999	IDF 2015
Essential criteria	None	IR (Impaired Fasting Glucose; Impaired glucose tolerance) or T2DM	Hyperinsulinemia 75th percentile	Central obesity: WC > 94 (m); > 80 (w) cm.
Criteria	3 out of 5 below	IR or diabetes + 2 out of 5 below	Hyperinsulinemia + 2 out of 4 below	Obesity + 2 out of 4 below
Obesity	WC >102 cm (man)	Waist/hip ratio > 0.9 (m); > 0.85 (w) or BMI> 30 kg/m^2	WC > 94 cm (m)	WC > 94 (m)
	Or > 88 cm (woman)		WC > 80 cm (w)	WC > 80 (w)
Hyperglycemia	FG > 5.6 mmol/l or use of anti-diabetics	IR required	IR required	FG > 5.6 mmol/L
Dyslipidemia	TG > 1.7 mmol/l; HDL < 1.0 mmol/l (m); or < 1.2 mmol/l (w) or use of anti-lipemics	TG > 1.7 mmol/l	TG > 2.0 mmol/l;	TG > 1.7 mmol/l; HDL < 1.0 mmol/l (m); or < 1.2 mmol/l (w) or use of anti-lipemics
		HDL < 0.9 mmol/l (m); or	HDL < 1.0 mmol/l man/woman	
		< 1.0 mmol/l (w)		
Hypertension	> 130/ > 85 mmHg or use of anti-hypertensives	>140/90 mm Hg	>140/90 mm Hg	> 130/> 85 mmHg or use of anti-hypertensives
Other criteria		Micro albuminuria ≥ 20 mg/l		
m = Man; w = Woman				

Table 4: *Definitions of metabolic syndrome.*

Results from assessment	Points
Weight gain despite several weight loss attempts	1
Chronic Stress	1
Sedentary Lifestyle	1
Sleep apnea: C-PAP or <6 hours sleep	1
High SBP or high Fasting Blood Glucose	1 point each
High WC according to ethnicity[1]	1
High FTG[2]; FTG/HDL-C[3]; or LDL/HDL-C[4] ratio	1
Chronic use of medication Antiepileptics Antipsychotics Betablockers Corticosteroids, all formulations Hormone therapy Insulin Pregabalin Statins SSRIs SU-derivatives	1 point each

Table 5: *IR diagnostic score card for adults > 4 points: IR present.*

[1]WC ≥ 94 cm man or ≥ 88 cm woman; Asians ≥ 90 cm man ≥ 80 cm woman; African Americans ≥ 102 cm man and ≥ 98 cm woman.

[2]FTG FTG: ≥ 1.78 mmol/l (men); ≥ 1.49 mmol/l (women); [3]FTG/HDL-C ratio ≥ 1.51 (men); ≥ 0.84 (women); [4]LDL-C/HDL-C ratio 3.80 (man); 3.82 (woman).

Discussion

In this exploratory review, we have summarized some of the evidence that explains how critical and destructive IR is with for numerous patients seen in primary and nutritional care. Many examples are cited in the medical literature that consistently call for reversing IR at the earliest possible stage. However, IR is still not "priority number one" addressed in day-to-day clinical practice. In this review, we summarize some of the evidence that IR may remain invisible, although present, for example, in apparently nonobese patients who develop T2DM or CVD at a later age. Moreover, we provide scientific arguments, that early detection and treatment of IR can prevent several related comorbidities. To be of service to practitioners to determine IR in daily practice, we propose a diagnostic tool to quantify this metabolic disorder. In this review we propose a tool to establish IR as a diagnosis by combining classical tools to assess IR indirectly with new evidence introduced by Taylor ea. who introduced "the personal fat threshold (PFT)". The PFT concept is a measure of the individual changes in insulin sensitivity related to weight gain, even in patients with a BMI < 25 kg/m^2 [68]. Several previously reported tools to

quantify IR combined with aging dynamics lend themselves perfectly to a combined composite diagnostic scorecard. We are concerned that by focusing only on weight loss, the essential IR concept is being overlooked. Many patients with failed weight loss attempts followed by subsequent gain fall victim to commercial diets. In our opinion, individual assessment of behavioral, physiological and physical criteria should be combined with tailored diets depending on the severity of the IR and comorbidities. Weight gain that is not fully understood by the patient needs further management by a qualified dietitian. The dietary approach to IR is a low carbohydrate high protein diet. Oppositely, there is no point in subjecting patients without IR to severe carbohydrate restrictions.

As mentioned earlier, studies are needed to find out the benefits of an early low-carb diet with the intention of restoring health. As a start, in 16 dietitian practices in the Netherlands, we conducted a study comparing patients with T2DM and severe IR comparing either a low-carbohydrate diet (< 50g carbohydrates) (LCHP); a 100g carbohydrate containing diet or a general energy restriction. Promising results were demonstrated in the LCHP arm of the study (24,3% of patients; ≥10% weight loss and 22,6%; between 5 - 10% weight loss) and a HbA1c reduction down to ≤ 43 mmol/mol in 38% of patients and a better quality of life in all patients [69].

Conclusion

Early recognition and treatment of IR as a clinical endpoint can reverse comorbidities later in life. To be successful, we must not reduce body weight in nutritional care according to guidelines, but strongly and sustainably suppress IR through tailor-made carbohydrate restriction. In a two-step approach, we encourage an active IR diagnosis and propose a dynamic tool for this to use in daily practice (the diagnostic scorecard; Table 5 this article). Based on previously reported research in national dietician practices, we have shown that tailor-made carbohydrate restriction is successful in severe IR patients. The condition for success in this study was that the registered dietitian is at the forefront. Future diagnostic and nutritional intervention studies are needed to bolster the evidence.

Conflict of Interest

The authors declare they have not been funded or sponsored to write the article.

Author Contributions

EG did the first selection on the literature and wrote the draft. DHS designed the article. IW corrected the manuscript. HV corrected the manuscript with special attention to technical details.

Bibliography

1. Reaven GM Diabetes. "Banting lecture 1988. Role of insulin resistance in human disease". 37 (1988): 1595-1607.
2. McLaughlin T., *et al*. "Prevalence of insulin resistance and associated cardiovascular disease risk factors among normal weight, overweight, and obese individuals". *Metabolism* 53.4 (2004): 495-499.
3. Salazar MR., *et al*. "Relationships among insulin resistance, obesity, diagnosis of the metabolic syndrome and cardio-metabolic risk". *Diabetes and Vascular Disease Research* 8.2 (2011): 109-116.
4. Brown J., *et al*. "Canadian Adult Obesity Clinical Practice Guidelines: Medical Nutrition Therapy in Obesity Management" (2020).
5. Saad MJA., *et al*. "Linking Gut Microbiota and Inflammation to Obesity and Insulin Resistance". *Physiology* 31 (2015): 283-293.
6. Kopeevich Mukhamedzhanov, E., *et al*. "Insulin Resistance - Pathogenesis of Prevention and Treatment". *Diabetes Complications* 2.4 (2018): 1-4.
7. Ghoshal S., *et al*. "Chylomicrons promote intestinal absorption of lipopolysaccharides". *Journal of Lipid Research* 50 (2009): 90-97.

8. Sturgeon C and Fasano A. "Zonulin, a regulator of epithelial and endothelial barrier functions, and its involvement in chronic inflammatory diseases". *Tissue Barriers* 4.4 (2016): e1251384.

9. Felger JC. "Imaging the Role of Inflammation in Mood and Anxiety-related Disorders". *Current Neuropharmacology* 16.5 (2018): 533-558.

10. Hardy AT., *et al*. "What causes the insulin resistance underlying obesity?" *Current Opinion in Endocrinology, Diabetes and Obesity* 19.2 (2012): 81-87.

11. Hotamisligil GS., *et al*. "Adipose expression of tumornecrosis factor-alpha: direct role in obesity-linked insulin resistance". *Science* 259 (1993): 87-91.

12. Galic S., *et al*. "Adipose tissue as an endocrine organ". *Molecular and Cellular Endocrinology* 316.2 (2010): 129-139.

13. Yang Q., *et al*. "Metabolites as regulators of insulin sensitivity and metabolism". *Nature Reviews Molecular Cell Biology* 19.10 (2018): 654-672.

14. Kim DH., *et al*. "Review. Adiponectin levels and the risk of hypertension: a systematic review and meta-analysis". *Hypertension* 62.1 (2013): 27-32.

15. Kalden J. "Emerging role of anti-tumor necrosis factor therapy in rheumatic diseases". *Arthritis Care and Research* 4.2 (2002): S34-40.

16. Zhang J and Shi GP. "Review Mast cells and metabolic syndrome". *Biochimica et Biophysica Acta* 1822 (2012): 14-20.

17. Caughey GH. "Mast cell tryptases and chymases in inflammation and host defense". *Immunological Reviews* 217 (2007): 141-154.

18. Xu H., *et al*. "Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance". *Journal of Clinical Investigation* 112 (2003): 1821-1830.

19. Okumura S., *et al*. "Identification of specific gene expression profiles in human mast cells mediated by Toll-like receptor 4 and Fc epsilon RI". *Blood* 102 (2003): 2547-2554.

20. Hara M., *et al*. "Evidence for a role of mast cells in the evolution to congestive heart failure". *Journal of Experimental* Medicine 195 (2002): 375-381.

21. Tsuruda T., *et al*. "Adrenomedullin in mast cells of abdominal aortic aneurysm". *Cardiovascular Research* 70 (2006): 158-164.

22. Kokkonen JO and Kovanen PT. "Stimulation of mast cells leads to cholesterol accumulation in macrophages in vitro by a mast cell granule-mediated uptake of low density lipoprotein". *Proceedings of the National Academy of Sciences of the United States of America* 84 (1987) 2287-2291.

23. Kokkonen JO and Kovanen PT. "Low-density-lipoprotein binding by mast-cell granules. Demonstration of binding of apolipoprotein B to heparin proteoglycan of exocytosed granules". *Biochemical Journal* 241 (1987): 583-589.

24. Liu J., *et al*. "Genetic deficiency and pharmacological stabilization of mast cells reduce diet-induced obesity and diabetes in mice". *Nature Medicine* 15 (2009): 940-945.

25. Okon K and Stachura J. "Increased mast cell density in renal interstitium is correlated with relative interstitial volume, serum creatinine and urea especially in diabetic nephropathy but also in primary glomerulonephritis". *Polish Journal of Pathology* 58 (2007): 193-197.

26. Würtz P., *et al*. "Branched-Chain and Aromatic Amino Acids Are Predictors of Insulin Resistance in Young Adults". *Diabetes Care* 36.3 (2013): 648-655.

27. León-Latre M., *et al*. "Aragon Workers' Health Study investigators. Sedentary lifestyle and its relation to cardiovascular risk factors, insulin resistance and inflammatory profile". *Revista Española de Cardiología* 67.6 (2014): 449-455.

28. Khaing Nang EE., *et al*. "Television screen time, but not computer use and reading time, is associated with cardio-metabolic biomarkers in a multiethnic Asian population: a cross-sectional study". *A Comparison of Two Short-Term Intensive Physical Activity* 10 (2013): 70.

29. Savas M., *et al*. "Systematic Evaluation of Corticosteroid Use in Obese and Non-obese Individuals: A Multi-cohort Study". *International Journal of Medical Sciences* 14.7 (2017): 615-621.

30. Savas M., *et al*. "Associations Between Systemic and Local Corticosteroid Use With Metabolic Syndrome and Body Mass Index". *The Journal of Clinical Endocrinology and Metabolism* 102.10 (2017): 3765-3774.

31. Leslie WS., *et al*. "Weight gain as an adverse effect of some commonly prescribed drugs: a systematic review". *QJM: An International Journal of Medicine* 100.7 (2007): 395-404.

32. McLaughlin T., *et al*. "Preferential fat deposition in subcutaneous versus visceral depots is associated with insulin sensitivity". *The Journal of Clinical Endocrinology and Metabolism* 96.11 (2011): E1756-1760.

33. Schadt EE., *et al*. "Identification and validation of N-acetyltransferase 2 as an insulin sensitivity gene". *Meta-Analysis Journal of Clinical Medicine* 125.4 (2015): 1739-1751.

34. Gast KB., *et al*. "Insulin resistance and risk of incident cardiovascular events in adults without diabetes: meta-analysis". *PLoS One* 7.12 (2012): e52036.

35. Wang F., *et al*. "Fasting insulin, insulin resistance and risk of hypertension in the general population: A meta-analysis". *Clinica Chimica Acta* 464 (2017): 57-63.

36. Lawlor DA., *et al*. "Independent associations of fasting insulin, glucose, and glycated haemoglobin with stroke and coronary heart disease in older women". *PLOS Medicine* 4.8 (2007): e263.

37. Yin DT., *et al*. "The association between thyroid cancer and insulin resistance, metabolic syndrome and its components: A systematic review and meta-analysis". *International Journal of Surgery* (2018);57 (2018): 66-75.

38. Hernandez AV., *et al*. "Insulin resistance and endometrial cancer risk: A systematic review and meta-analysis". *European Journal of Cancer* (2015).

39. Carreras-Torres R., *et al*. "The Role of Obesity, Type 2 Diabetes, and Metabolic Factors in Pancreatic Cancer: A Mendelian Randomization Study. Meta-Analysis". *Journal of the National Cancer Institute* 109.9 (2017): djx012.

40. Saboori S., *et al*. "Serum insulin level, HOMA-IR and prostate cancer risk: A systematic review and meta-analysis". *Meta-Analysis Diabetes and Metabolic Syndrome* 13.1 (2019): 110-115.

41. Albanes D., *et al*. "Serum insulin, glucose, indices of insulin resistance, and risk of prostate cancer". *Journal of the National Cancer Institute* 101.18 (2009): 1272-1279.

42. Xu J., *et al*. "Association between markers of glucose metabolism and risk of colorectal cancer". *Review BMJ Open* 6.6 (2016): e011430.

43. Esposito K., *et al*. "Metabolic syndrome and postmenopausal breast cancer: systematic review and meta-analysis". *Review Menopause* 20.12 (2013): 1301-1309.

44. Vigneri R., *et al*. "Review Insulin, insulin receptors, and cancer". *Journal of Endocrinological Investigation* 39 (2016): 1365-1376.

45. Behboudi-Gandevani S., *et al*. "Insulin resistance in obesity and polycystic ovary syndrome: systematic review and meta-analysis of observational studies". *Review Gynecological Endocrinology* 32.5 (2016): 343-353.

46. Lerchbaum E., *et al*. "Influence of a positive family history of both type 2 diabetes and PCOS on metabolic and endocrine parameters in a large cohort of PCOS women". *European Journal of Endocrinology* 170.5 (2014): 727-739.

47. Napolitano M., *et al*. "Insulin Resistance and Skin Diseases". *Scientific World Journal* (2015): 479354.

48. Zhu H-C., *et al*. "Correlations of insulin resistance and HbA1c with cytokines IGF-1, bFGF and IL-6 in the aqueous humor of patients with diabetic cataract". *Observational Study European Review for Medical and Pharmacological Sciences* 23.1 (2019): 16-22.

49. Watt MJ., *et al*. "The Liver as an Endocrine Organ-Linking NAFLD and Insulin Resistance". *Endocrine Reviews* 40.5 (2019): 1367-1393.

50. Pais R., *et al*. "Prevalence of steatosis and insulin resistance in patients with chronic hepatitis B compared with chronic hepatitis C and non-alcoholic fatty liver disease". *European Journal of Internal Medicine* 26.1 (2015): 30-36.

51. De la Monte SM. "Insulin Resistance and Neurodegeneration: Progress Towards the Development of New Therapeutics for Alzheimer's Disease". *Drugs* 77.1 (2017): 47-65.

52. Crofts C., *et al*. "Identifying hyperinsulinaemia in the absence of impaired glucose tolerance: An examination of the Kraft database". *Diabetes Research and Clinical Practice* 118 (2016): 50-57.

53. Wallace TM., *et al*. "Use and abuse of HOMA modeling". *Diabetes Care* 27.6 (2004): 1487-1495.

54. Kurtoğlu S., *et al*. "Insulin resistance in obese children and adolescents: HOMA-IR cut-off levels in the prepubertal and pubertal periods". *Journal Of Clinical Research İn Pediatric Endocrinology* 2.3 (2010): 100-106.

55. Katz A., *et al*. "Quantitative insulin sensitivity check index: a simple, accurate method for assessing insulin sensitivity in humans". *The Journal of Clinical Endocrinology and Metabolism* 85.7 (2000): 2402-2410.

56. McAuley KA., *et al*. "Diagnosing Insulin Resistance in the General Population". *Diabetes Care* 24.3 (2001): 460-464.

57. Ter Horst KW., *et al*. "Insulin resistance in obesity can be reliably identified from fasting plasma insulin". *International Journal of Obesity* 39.12 (2015): 1703-1709.

58. Polonsky KS., *et al*. "Twenty-four-hour profiles and pulsatile patterns of insulin secretion in normal and obese subjects". *Journal of Clinical Investigation* 81.2 (1988): 442-448.

59. Zhang L., *et al*. "Association between lipid ratios and insulin resistance in a Chinese population 10.1 (2015): e0116110.

60. American Heart Association (2021).

61. Chou H-H., *et al*. "Insulin resistance is associated with C-reactive protein independent of abdominal obesity in nondiabetic Taiwanese". *Metabolism* 59.6 (2010): 824-830.

62. Lu B., *et al*. "Insulin resistance in Chinese patients with type 2 diabetes is associated with C-reactive protein independent of abdominal obesity". *Cardiovascular Diabetology* 9 (2010): 92.

63. Sumner AE., *et al*. "Determining the waist circumference in African Americans which best predicts insulin resistance". *Obesity* 16.4 (2008): 841-846.

64. Verkouter I., *et al*. "The Association between Adult Weight Gain and Insulin Resistance at Middle Age: Mediation by Visceral Fat and Liver Fat". *Journal of Clinical Medicine* 8.10 (2019): 1559.

65. Sun W., *et al*. "Association between the change in body mass index from early adulthood to midlife and subsequent type 2 diabetes mellitus". *Obesity* 24 (2016): 703-709.

66. Zhu Y., *et al*. "Mid-upper arm circumference as a simple tool for identifying central obesity and insulin resistance in type 2 diabetes". *PLoS ONE* (2020): e0231308.

67. Hou Y., *et al*. "Association between mid-upper arm circumference and cardiometabolic risk in Chinese population: a cross-sectional study". *BMJ Open* 9 (2019): e028904.

68. Taylor R and Holman RR. "Normal weight individuals who develop type 2 diabetes: the personal fat threshold". *Clinical Science* 128.7 (2015): 405-410.

69. Govers E., *et al*. "Effectiveness of a Very Low Carbohydrate Ketogenic Diet Compared to a Low Carbohydrate and Energy-Restricted Diet in Overweight/Obese Type 2 Diabetes Patients". *International Journal of Endocrinology and Metabolic Disorders* 5.2 (2019).

Volume 16 Issue 7 July 2021