WHITE PAPER

Assessing Insulin Resistance and the Risk of Type 2 Diabetes: Beyond Fasting Glucose

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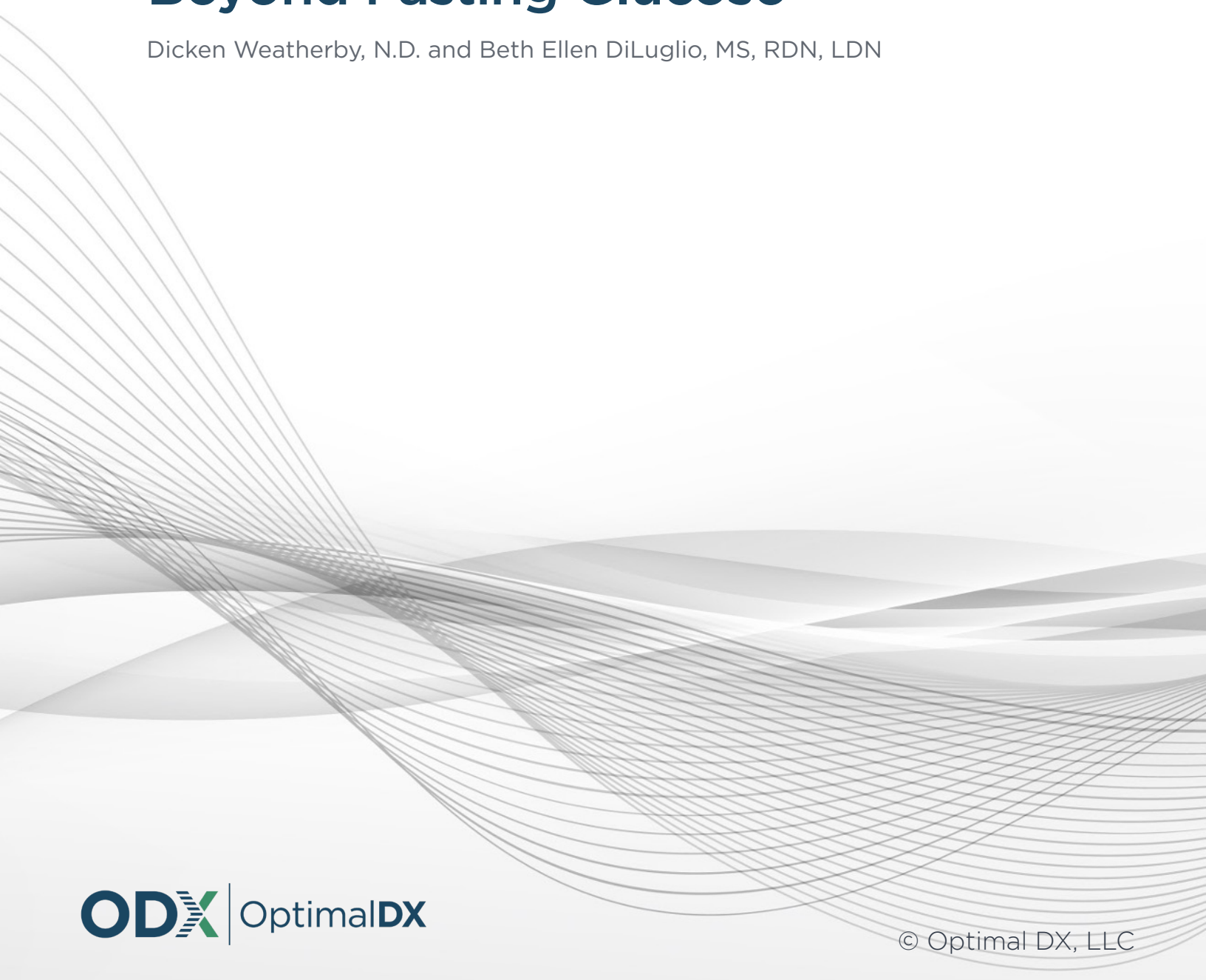

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Abstract

Blood glucose dysregulation is at epidemic proportions, especially insulin resistance, hyperglycemia, and their final manifestation, type 2 diabetes mellitus (T2DM).

Worldwide, nearly half-a billion people have diabetes, that's nearly 10% of the global population. Prevalence is expected to reach 700 million by the year 2045.[1]

In the United States alone there are more than 34.2 million people living with significant dysglycemia in the form of T2DM, accounting for 10.5% of the 2020 US population. An estimated 7.3 million of these are undiagnosed. Another 88 million adults have prediabetes, accounting for 34.5% of the US population.[2]

This is a notable increase from 2017 statistics when 30 million people (9.5% of the population) were living with T2DM, and another 86 million (34% of the population) were pre-diabetic.[3] The CDC estimates that 84% of those with prediabetes are unaware that they have it.

We are going in the wrong direction.

These statistics mean that nearly half of the US population has advanced blood glucose dysregulation and is at significant risk of related complications including cardiovascular disease, stroke. blindness, kidney failure, amputation, and non-alcoholic fatty liver disease (NAFLD). As the seventh leading cause of death in the United States with an annual price tag of $237 billion in healthcare spending, diabetes exacts a heavy personal and economic toll.[4] [5]

That is unacceptable.

Type 2 diabetes does not develop overnight. It is the culmination of modifiable risk factors such as obesity, insulin resistance, metabolic syndrome, and fatty liver,[6] along with their risk factors of sedentary lifestyle, nutrient-poor diet, exposure to environmental toxins, smoking, alcohol consumption, and chronic inflammation.[7] [8]

If we walk back a few steps, we find that insulin resistance is likely the long fuse that leads to the T2DM powder keg. Early identification of impaired glucose tolerance and progressive insulin resistance is necessary if the epidemic of diabetes is to be brought under control. This can be accomplished with skillful investigation of early biochemical changes as part of a functional blood chemistry analysis.

Introduction

While the risk factors for T2DM are well understood, and screening tests to identify elevated blood glucose levels exist, research is beginning to demonstrate that uncontrolled blood glucose may be secondary to insulin resistance in some circumstances. In such cases, by the time abnormal blood glucose levels are identified via laboratory investigation, the pathophysiologic changes of diabetes have already begun.[9] [10]

Identifying the physiologic abnormalities related to insulin resistance earlier would make it possible to intervene sooner, therefore increasing the likelihood of preventing disease development and/or slowing disease progression.

This review will address

- Insulin biochemistry and physiology
- Insulin resistance and the road to diabetes
- Comorbidities and conditions associated with insulin resistance
- Biomarker profiles associated with insulin resistance
- HOMA2 and QUICKI calculations for assessing insulin resistance
- Further down the road to type 2 diabetes
- Lifestyle and nutrition intervention to address and reverse insulin resistance

Insulin Biochemistry and Physiology

Let's have a brief look at the biochemistry and physiology of insulin.

Insulin is a peptide hormone produced and secreted by the Islets of Langerhans beta cells in the pancreas. It has anabolic actions that lower blood glucose and affect lipid and protein metabolism. Insulin promotes synthesis of glycogen, protein, and lipids. It also promotes cell division and growth.[11]

Insulin has a direct effect on:[12]

- Muscle
    - Increases glucose transport and utilization, and stimulates glycogen synthesis and storage
- Liver cells
    - Stimulates glycogen synthesis and lipid storage
    - Reduces gluconeogenesis and hepatic glucose production
    - Decreases availability of circulating fatty acids
- White adipose tissue
    - Increases glucose transport and lipogenesis and decreases lipolysis

Pancreatic beta cells are able to store a small amount of insulin that can be released quickly when blood glucose rises. A reduction in insulin release at this point indicates beta cell dysfunction and predicts an increased likelihood of developing type 2 diabetes.[13] [14] [15]

Insulin Resistance, the Road to Diabetes, and Stops Along the Way

The road to insulin resistance and diabetes is paved with processed food, added sugar, toxins, micronutrient insufficiencies, and a sedentary lifestyle.

This same path can lead to other complications including cardiovascular disease, metabolic syndrome, polycystic ovary syndrome (PCOS), and non-alcoholic liver disease (NAFLD).[16]

The presence of NAFLD is a particularly glaring factor as it is present in ~60-70% of individuals with T2DM. NAFLD comprises early non-alcoholic fatty liver (NAFL), nonalcoholic steatohepatitis (NASH), and cirrhosis.[17]

But which came first, the NAFLD or T2DM? They share important risk factors including obesity, insulin resistance, and metabolic syndrome. NAFLD is so closely tied to metabolic syndrome that it is considered the hepatic manifestation of this common disorder.

So, no matter which came first, it is most important to focus on and resolve these major risk factors, especially insulin resistance which can be invisible and asymptomatic.

Even in those with normal glucose tolerance, the presence of insulin resistance (and its major risk factors of hyperinsulinemia, increased body fat, obesity, and sedentary lifestyle) is predictive of type 2 diabetes development.[18]

Insulin Resistance

Insulin resistance is considered an early sign in the development of type 2 diabetes. It is characterized by an inability to reduce elevated blood glucose in the face of normal plasma insulin. This phenomenon often accompanies chronic excess intake of calories, carbohydrates, and fats.

While some cases of insulin resistance have a genetic component, most cases are acquired due to:[19]

- ✓ Aging
- ✓ Excess dysfunctional adipose tissue
- ✓ Glucose toxicity
- ✓ Increased sodium diets*
- ✓ Lipotoxicity from excess circulating free fatty acids
- ✓ Medications (glucocorticoids, anti-adrenergic, protease inhibitors, atypical antipsychotics, and some exogenous insulin)
- ✓ Nutritional imbalance
- ✓ Physical inactivity
- ✓ *Note contrary to the assumption that high sodium intake increases insulin resistance, research published in 2011 found that a low-salt, versus a high-salt diet, was significantly associated with increased insulin resistance in healthy subjects. Low salt intake correlated with a significantly higher homeostatic model assessment value (HOMA). Serum aldosterone, as well as urinary aldosterone and norepinephrine were significantly higher on the low-salt diet as well.[20]

In the event of insulin resistance, target tissues (e.g., muscle, liver, adipose tissue) don't respond normally to insulin.[21]

Physiologically, there will be a decrease in glucose uptake, glucose oxidation, and glycogen synthesis. With insulin resistance, there will also be less suppression of lipolysis in adipocytes so lipid oxidation increases.[22] Endogenous production of glucose will continue and won't be suppressed as would ordinarily occur with normal insulin sensitivity.

As insulin resistance persists, plasma insulin levels continue to rise to compensate for elevated glucose and cellular resistance, eventually leading to lipid and glucose toxicity and beta cell failure.

Ultimately, peripheral insulin resistance is the major factor contributing to metabolic syndrome and its progression to type 2 diabetes.[23]

Insulin resistance[24]

Insulin resistance is identified as

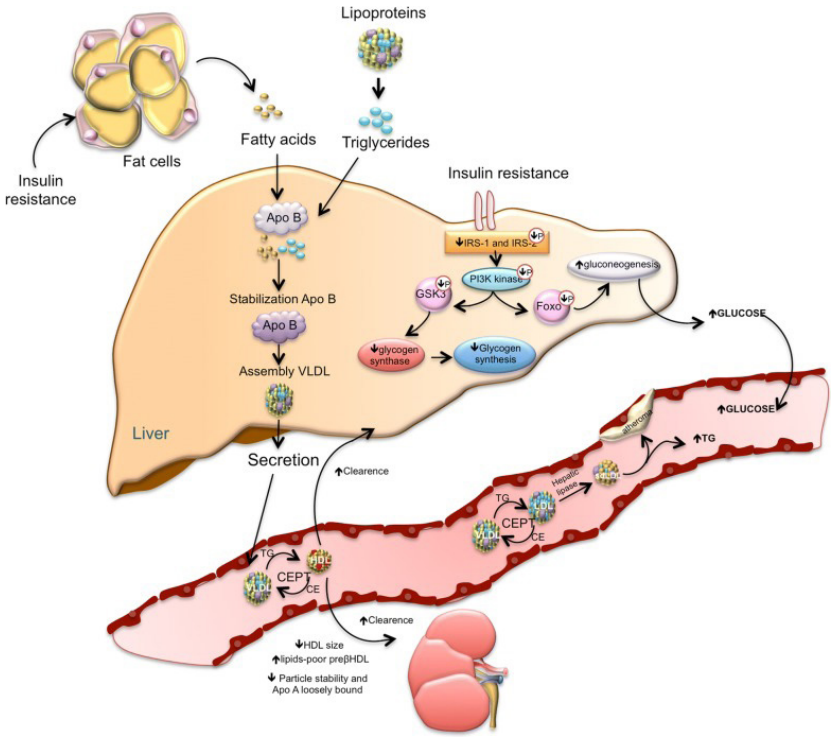
- ✓ An impaired biologic response to insulin stimulation of target tissues, primarily the liver, muscle, and adipose tissue.
- ✓ Insulin resistance impairs glucose disposal, resulting in a compensatory increase in beta-cell insulin production and hyperinsulinemia.
- ✓ Insulin resistance is primarily an acquired condition related to excess body fat, though genetic causes are identified as well.

The metabolic consequences of insulin resistance can result in

- ✓ Hyperglycemia, hypertension, dyslipidemia, visceral adiposity, hyperuricemia, elevated inflammatory markers, endothelial dysfunction, and a prothrombotic state.
- ✓ Progression of insulin resistance can lead to metabolic syndrome, nonalcoholic fatty liver disease, and type 2 diabetes mellitus.

"Even without hyperglycemia, the presence of insulin resistance and beta cell dysfunction increases the risk for cardiovascular disease, retinopathy, neuropathy, microalbuminuria, certain cancers, pulmonary disease, depression, dementia, hospitalization, and early death."[25]

A Simplified Model of Insulin Resistance



The loss of suppressive effects of insulin on lipolysis in adipocytes increases free fatty acids. Increased free fatty acids flux to the liver stimulates the assembly and secretion of VLDL resulting in hypertriglyceridemia. Triglycerides (TG) in VLDL are transferred to both HDL and LDL through the action of cholesteryl ester transfer protein (CETP). This process results in a triglyceride-enriched HDL and LDL particle. Triglyceride-enriched HDL is more rapidly cleared from the circulation by the kidney, leaving fewer HDL particles to accept cholesterol from the vasculature. In the glucose metabolism, the insulin resistance results in decreased hepatic glycogen synthesis, owing to decreased activation of glycogen synthase, increased hepatic gluconeogenesis, and glucose delivery by the liver.

Source: Ormazabal, Valeska et al. "Association between insulin resistance and the development of cardiovascular disease." Cardiovascular diabetology vol. 17,1 122. 31 Aug. 2018, doi:10.1186/s12933-018-0762-4 [R] Open Access This article is distributed under the terms of the Creative Commons Attribution 4.0 International License ([R]).

Inflammation

It is not surprising that chronic inflammation may trigger insulin resistance, as evidenced by its association with inflammatory biomarkers.[26]

Research suggests that early signs of subclinical inflammation may precede and predict insulin resistance. This appears to be especially true of hepatic insulin resistance which is associated with early beta cell upregulation. Evaluation of data from the Whitehall II study revealed that increased fasting insulin and insulin resistance were associated with increased systemic inflammation reflected by increased hs-CRP and IL-6, and decreased adiponectin.[27]

An even more sensitive marker of systemic inflammation is emerging, called GlycA (glycoprotein acetylation). GlycA appears to be more sensitive than hs-CRP for identifying and monitoring systemic inflammation.

An elevated level of GlycA has a robust correlation with plasma glucose and insulin resistance and is considered predictive of incident T2DM.[28] [29]

Cardiovascular Disease

Insulin resistance is considered a major risk factor for the development of dyslipidemia, hypertension, and atherosclerosis, and is a likely risk factor for stroke and coronary heart disease.[30] It is a major contributor to cardiovascular disease (CVD) in type 2 diabetes.

Physiologically, hyperinsulinemia and insulin resistance exert adverse effects on several cardiovascular indices including platelet function, coagulation, blood pressure, endothelial function, and lipid profiles.[31]

Insulin resistance in general has long been recognized as a metabolic disorder and risk factor for CVD. A detailed review from 1991 notes that[32]

- ✓ Insulin resistance is directly related to severity of hypertension and appears to be the connection between essential hypertension and diabetes.
- ✓ Even in normal weight individuals, an exaggerated insulin response to glucose is observed in those with hypertension.
- ✓ Insulin is noted to be atherogenic as it increases cholesterol transport into arterioles where it also enhances lipid synthesis, stimulates cell proliferation, and promotes plaque formation.

At present, insulin resistance is gaining greater recognition as a comorbidity in CVD, especially when considering:[33]

- ✓ Chronic hyperglycemia contributes to damaging oxidative stress and inflammation.
- ✓ Insulin resistance promotes atherogenic dyslipidemia characterized by hypertriglyceridemia, low HDL, and increased small dense LDL.
- ✓ Insulin resistance can directly damage myocardial cells and cause endothelial dysfunction.
- ✓ Insulin inhibits use of fatty acids in the cardiomyocyte, leading to a buildup of lipids and lipotoxicity. Fatty acids are the heart's preferred source of energy, ordinarily providing 50-70% of its ATP needs.

Oxidative stress is a common characteristic of CVD. The presence of chronic oxidative stress, along with dyslipidemia and hyperglycemia, has particularly detrimental effects on beta cells which have high oxidative requirements. Consequences include decreased beta cell gene expression, beta cell death, and impaired glucose tolerance.[34]

Once T2DM has developed, diabetic cardiovascular autonomic neuropathy (DCAN) can significantly impact health and longevity. Research reveals a cutoff point for HOMA2-IR of 1.735 for DCAN, with a progressive increase as the condition worsens.[35]

Assessing Insulin Resistance Risk, Signs, and Symptoms

It is essential to identify insulin resistance early as it can precede overt diabetes by several years.[36]

Risk factors and comorbidities for insulin resistance include[37] [38] [39] [40] [41] [42] [43]

- ✓ Abnormal uric acid metabolism
- ✓ Age over 40 years old
- ✓ Alcohol intake
- ✓ Dyslipidemia
- ✓ Endothelial dysfunction
- ✓ Family history of T2DM, hypertension, or CVD
- ✓ Hyperinsulinemia, fasting insulinemia
- ✓ Hypertension
- ✓ Glucose intolerance, impaired fasting glucose
- ✓ Inflammatory markers
- ✓ Metabolic syndrome
- ✓ Non-Caucasian ethnicity
- ✓ Obesity, particularly abdominal/visceral obesity
- ✓ Poor diet in the prenatal and early postnatal periods
- ✓ Prothrombotic factors
- ✓ Metabolic acidosis and acidogenic diet[44]
- ✓ Sedentary lifestyle
- ✓ Smoking
- ✓ Toxins, pesticides, air pollution

Insulin resistance may have no symptoms initially. However, early signs may include: [45] [46] [47] [48] [49]

- ✓ Acanthosis nigricans (darkened skin patches)
- ✓ Difficulty concentrating
- ✓ Elevated cholesterol
- ✓ Hunger
- ✓ Hypertension
- ✓ Lethargy
- ✓ Microalbuminuria
- ✓ Weight gain, especially around the abdomen
- ✓ Advanced, severe uncontrolled hyperglycemia can manifest as
  - Polyuria, polydipsia, weight loss
  - Metabolic acidosis, low bicarbonate, increased anion gap

Insulin resistance is also associated with other disorders including[50]

- ✓ Acromegaly
- ✓ Atherosclerosis
- ✓ Autoantibodies against the insulin receptor
- ✓ Coronary artery disease
- ✓ Dyslipidemia
- ✓ Genetic insulin receptor disorders
- ✓ Glucocorticoid excess
- ✓ Hyperlipidemia
- ✓ Hypertension
- ✓ Infection
- ✓ Obesity
- ✓ Polycystic ovary syndrome
- ✓ Pregnancy
- ✓ Stress
- ✓ Stroke
- ✓ Uremia

Insulin resistance is becoming more common though less obvious in seemingly healthy individuals. Both insulin resistance and metabolic syndrome pave the way to type 2 diabetes.

Even In young subjects ages 8-19 years old, increased insulin resistance was significantly associated with central obesity, high blood pressure, elevated triglycerides, low HDL, decreased adiponectin, and impairments in glucose tolerance and fasting glucose.[51]

Insulin Resistance and the Brain

Both human and animal research suggest that insulin plays an important role in brain metabolism, synaptic viability, neurotransmitter turnover, and possibly amyloid beta peptide clearance.[52]

While peripheral insulin resistance leads to T2DM, insulin resistance in the brain can lead to the cognitive impairment and neuronal dysfunction seen in Alzheimer's disease.[53]

Assessing Insulin Resistance – The Biomarkers [54]

Biomarker evidence is likely to be the first clinical sign of developing insulin resistance, followed by worsening metabolic control, hyperglycemia, and physical manifestations.

Fasting Glucose:

- ✓ Elevated in impaired glucose tolerance, prediabetes, diabetes
- ✓ Fasting glucose reflects hepatic production of glucose while 2-hour glucose reflects uptake of glucose in the periphery.[55]

Fasting Insulin:

- ✓ Elevated in insulin resistance

Adiponectin:

- ✓ Inversely associated with fasting glucose, fasting insulin, homeostasis model assessment for insulin resistance (HOMA-IR), beta cell function, and HbA1C. Levels may drop quickly prior to development of type 2 diabetes.

Inflammatory Markers

- ✓ Hs- CRP:
  - Elevated in impaired glucose tolerance, prediabetes, and diabetes though may not have an independent association.
- ✓ IL-6
  - Associated with elevated fasting insulin, insulin resistance, and beta cell function
  - Elevated in diabetes
- ✓ GlycA[56]
  - Elevated in inflammation and insulin resistance, predictive of T2DM
- ✓ Tumor necrosis factor alpha (TNF-alpha)[57]
  - TNF-alpha, primarily produced in adipose tissue, monocytes, and lymphocytes, increases free fatty acid release from adipocytes, blocks adiponectin synthesis, and disrupts receptor activity.

Triglycerides

Hypertriglyceridemia may serve as a predictor of insulin resistance as it significantly correlated with fasting insulin, homeostasis model assessment, and metabolic syndrome in subjects with an increased waist circumference (greater than 102 cm for males, greater than 85 cm for females).[58]

In a cohort study of Manitoba First Nation individuals, elevated fasting triglycerides were significantly associated with changes in insulin resistance and incident diabetes. Those with fasting triglycerides 187 mg/dL (2.11 mmol/L) or greater had a 4 times greater risk of diabetes than those with a fasting triglyceride level of less than 120 mg/dL (1.36 mmol/L).[59]

Insulin resistance contributes to an increase in serum triglycerides because it inhibits muscle cells from taking up triglycerides (and glucose) from circulation. Resultant hyperglycemia can also damage muscle cells directly, causing further declines in physical function and insulin sensitivity.[60]

Branched Chain Amino Acids

Research suggests that insulin resistance promotes measurable increases in circulating levels of amino acids, especially branched-chain amino acids (BCAAs- leucine, isoleucine, valine) which are in turn associated with risk of T2DM. Underlying causes of this phenomenon may be genetic and not related to dietary intake of BCAAs.[61]

In fact, dietary BCAAs have been associated with positive effects including muscle protein synthesis, glucose homeostasis, and regulation of body weight and body composition. It appears that elevated fasting levels of BCAAs may reflect metabolic dysregulation in those with obesity and increased risk of T2DM.[62] [63]

Insulin has an inhibitory effect on the release of BCAAs from skeletal muscle. Blood levels of BCAAs increase sharply and significantly in the absence of insulin (or its effects) as occurs in diabetic ketoacidosis.[64]

Researchers suggest that circulating BCAAs may serve as a biomarker for evaluating risk of T2DM.[65]

C-peptide[66]

C-peptide reflects beta cell function and is a measure of insulin secretion. It is cleaved from proinsulin prior to insulin secretion so production and concentrations mirror those of insulin itself.

Elevated levels are associated with insulin resistance, metabolic syndrome risk, cardiovascular disease, and all-cause mortality. Lower levels are associated with increased glucose variability.

C-peptide below 0.6 ng/mL (0.2 nmol/L) is diagnostic of type 1 diabetes mellitus due to reduced insulin production.

Levels should be measured in the fasting state as post-prandial levels can increase in healthy individuals from 0.9-1.81 ng/mL (0.3-0.6 nmol/L) to 3-9 ng/mL (1-3 nmol/L).

Alpha-hydroxybutyrate (a-HB):

Alpha-hydroxybutyrate is an early marker for insulin resistance and impaired glucose tolerance. Elevations in a-HB appear to be related to oxidative stress, altered lipid metabolism, amino acid catabolism, and increased demand for hepatic glutathione. A plasma a-HB of 5 ug/mL or greater suggests insulin resistance and impaired glucose tolerance.[67]

Research demonstrates that a-HB: [68]

- ✓ Significantly correlates with
    - fasting glucose, fasting insulin, HOMA-IR, BMI, body fat distribution, waist circumference, waist-to-hip ratio, triglycerides, total cholesterol, and LDL cholesterol, despite the absence of cardiometabolic disease
- ✓ May be a marker for worsening metabolic profiles in those with low risk of diabetes who are nonobese and normotensive
- ✓ Is inversely correlated with beta cell function
- ✓ May detect subclinical hyperglycemia and prediabetes
- ✓ May identify insulin resistance in the absence of traditionally recognized risk factors
- ✓ Reflects an increase in lipid oxidation, a pathological characteristic of insulin resistance
- ✓ Is generated during production of endogenous antioxidants, including glutathione.

- ✓ Positively correlates with total cholesterol, liver enzymes, and blood pressure
- ✓ Increases as cardiovascular risk factors increase, even when these parameters are within standard range

In a cross-sectional study of 217 individuals, fasting glucose, fasting insulin, C-peptide, and 1-hour and 2-hour glucose were significantly higher in those with an a-HB below 3.9 ug/mL. Hemoglobin A1C was not significantly different in those with a-HB below 3.9 ug/mL (5.3%) versus those with a-HB of 3.9 ug/mL or above (5.5%), suggesting that a-HB is a better early indicator of subclinical hyperglycemia and beta cell dysfunction.[69]

Research also recommends further evaluation of OGTT, suggesting a 1-hour glucose of 155 mg/dL (8.6 mmol/L) or greater be considered prediabetes.[70]

HOMA2 and QUICKI: Indices for Assessing Insulin Resistance

Insulin sensitivity reflects the responsiveness of peripheral tissues to insulin and their ability to take up circulating glucose. When cells are less responsive to insulin, beta cells produce more insulin to compensate, creating a vicious cycle of increased production and increased resistance.

Insulin sensitivity can be measured and should be assessed in patients at high risk for glucose dysregulation. These new measurements are preferred to traditional invasive measurements.

Traditional Assessment of Insulin Sensitivity

The current gold standard measurement for assessing insulin sensitivity and insulin secretion capacity utilizes the hyperinsulinemic-euglycemic clamp and the hyperglycemic clamp or the intravenous glucose tolerance test. However, both tests are invasive, and neither is convenient to use for screening or population-wide assessment.[71]

The oral glucose tolerance test (OGTT) is the current clinical tool used by primary care providers to assess for diabetes, insulin resistance, and impaired beta cell function. However, it does not have the capacity to distinguish between peripheral insulin resistance and a reduced capacity of the pancreatic beta cell to produce insulin, nor does it accurately reflect disease progress or severity of disease sequelae. Both the American Diabetes Association and the World Health Organization find it to be an unreliable stand-alone test and recommend the OGTT be repeated twice before a diagnosis can be made.[72]

Researchers also point out that hemoglobin A1C and fasting plasma glucose have even lower sensitivity for diagnosing diabetes than OGTT and should not be used as stand-alone diagnostic tests using current classification criteria.[73]

It is becoming clear that the epidemic of diabetes and associated dysglycemic conditions is out of control, and the old way of assessing dysglycemia and diabetes is not clinically useful; a new method is needed.

Homeostasis Model Assessments (HOMA)

The HOMA calculator is a tool used to estimate beta cell function and the degree of insulin sensitivity based on the following biomarkers: fasting blood glucose, fasting insulin and/or C-peptide.

The original HOMA calculator was formulated in 1985 and updated in 1998 to the model currently in use, which is called the HOMA2 calculator. HOMA2 takes into account proinsulin secretion as well as variances in both hepatic and peripheral glucose resistance.[74] [75]

Research confirms that HOMA2 is a better predictor of progression to diabetes than the original HOMA1.[76] HOMA2 is a complex mathematical model of the physiologic processes that influence circulating glucose and insulin levels. It is used to estimate beta cell function (HOMA2-%B), insulin sensitivity (HOMA2-%S) and insulin resistance (HOMA2-IR).[77]

Measurements of these biomarkers are quickly and easily attained, and research shows that HOMA2-IR and HOMA2-%B calculations show good correlation with the values obtained by the aforementioned gold standard tests.[78]

HOMA2

Beta cell function, insulin sensitivity, and insulin resistance

The beta cells of the pancreatic islets are responsible for production and secretion of insulin. Beta cells have a small capacity to store insulin. The stored insulin is secreted immediately upon elevation of blood glucose levels, causing a short-term increase in blood insulin levels. Reduced insulin release in this initial phase is the earliest known detectable indicator of beta cell dysfunction and is an independent predictor of T2DM.[79]

Insulin sensitivity is a term used to indicate the responsiveness of peripheral tissue cells to insulin, and their resultant capacity to take glucose out of the bloodstream. In patients with chronically elevated serum insulin, peripheral tissue cells become less sensitive to insulin, and therefore require that more insulin be secreted in order to take up the same amount of glucose and return serum glucose levels back to normal. This stage is called insulin resistance.

In patients with insulin resistance, beta cells respond by secreting increasing amounts of insulin in order to return glucose to normal. Chronic insulin resistance is typically seen as a component of prediabetes. If left untreated, insulin resistance will result in decreased beta cell function, eventually progressing to loss of the capacity to produce and secrete insulin, and the development of T2DM.

The HOMA2 calculator estimates insulin sensitivity and beta cell function from fasting glucose levels and either fasting insulin or C-peptide.

It is calibrated based on population norms, and provides a measure of insulin resistance, HOMA2-IR, which will be 1 in an individual with no insulin resistance.

It is also a measure of beta cell function, HOMA2-%B, which will be 100% in an individual with normal beta cell function.

The capacity of peripheral tissue to respond to insulin appropriately is expressed as HOMA2-%S (sensitivity), where the higher the HOMA-%S value, the more responsive the cells are to insulin. Evidently, the HOMA2-%S measurement is directly linked to the level of insulin resistance (HOMA2-IR). As such, assessment of HOMA2-%S without also assessing HOMA2-IR will not give a complete picture of metabolic function.

As insulin resistance increases, HOMA2-%S (sensitivity) will decrease, and HOMA2-IR (resistance) will increase.

HOMA2-IR

- Standard range: 0.5-1.75 Index
- Optimal range: 0.75-1.25 Index

HOMA2-IR Summary

- ✓ Estimates insulin resistance
- ✓ **HOMA2-IR will be 1** in those with no insulin resistance
- ✓ HOMA2-IR and HOMA2-%B will both be elevated early in insulin resistance, prediabetes, and early T2DM
- ✓ Elevated HOMA2-IR and decreasing HOMA2-%B can be seen as beta cells start to fail and produce less insulin

Elevated HOMA2-IR is indicative of increasing levels of insulin resistance in peripheral tissue. This is commonly seen in prediabetes and T2DM. Insulin resistance and elevated HOMA2-IR measures are secondary to elevated insulin levels, which is usually a result of elevated serum blood glucose levels.

An elevated HOMA2-IR measure would be seen in conjunction with an elevated HOMA2-%B measurement in prediabetes, or perhaps early stages of T2DM. Elevated HOMA2-IR would be seen in conjunction with a decreased HOMA2-%B measurement once the disease has progressed to the point of beta cell failure.

HOMA2-IR may vary at different stages of insulin resistance.

There are no absolute values for HOMA indices due to potential variations in lab assays for glucose, insulin, and C-peptide.[80] Ongoing research has helped to define cutoffs above which insulin resistance and metabolic syndrome are likely.

	Emerging research	
2004[81]	HOMA2-IR greater than 1.47 identifies metabolic syndrome or early stage insulin resistance	
	HOMA2-IR greater than 1.87 identifies insulin resistance	
2008[82]	Greater than 1.67 may indicate insulin resistance	
2009[83]	Greater than 1.4 identified metabolic syndrome	
	Greater than 1.8 identified insulin resistance	
2015[84] Women	HOMA2-IR	1.41 or greater increased risk of incident T2DM
	HOMA-2%S	72,5 or less increased risk of incident T2DM
	HOMA2-%B	63.7 or less increased risk of incident T2DM
	Insulin	11.13 uU/mL or greater increased risk of incident T2DM
Men	HOMA2-IR	1.18 or greater increased risk of incident T2DM
	HOMA-2%S	74.6 or less increased risk of incident T2DM
	HOMA2-%B	74,1 or less increased risk of incident T2DM
	Insulin	9.16 uU/mL or greater increased risk of T2DM
2016[85]	HOMA2-IR	1.27 in normal glucose tolerance group
		1.46 in prediabetic group
	HOMA2-%B	100 in normal glucose tolerance group
		93 in prediabetic group
2020[86]	1.4 considered optimal threshold for identifying insulin resistance	
2020[87]	HOMA2-IR	1.69 or greater suggests insulin resistance, metabolic syndrome risk
	HOMA-2%S	53.9 or less suggests insulin resistance, metabolic syndrome risk
	HOMA2-%B	87.12 or less suggests insulin resistance, metabolic syndrome risk
	QUICKI	0.32 or less suggests insulin resistance, metabolic syndrome risk

HOMA2-%B

- Standard range 70-120%
- Optimal range 90-110%

HOMA2-%B Summary

- ✓ Estimates beta cell function, an increase reflects increased beta cell activity
- ✓ Will be 100% with normal beta cell function and no insulin resistance
- ✓ Increases as insulin increases but will decrease after prolonged elevated insulin levels, reflecting beta cell failure
- ✓ Is linked to insulin sensitivity and will change in response to changes in HOMA2-S% in non-diabetics.
- ✓ Diabetic patients are unable to compensate with an increase in beta cell function/HOMA2-%B. Therefore HOMA2-S% and HOMA2-%B must be evaluated together.[88]
- ✓ Elevated HOMA2-%B and elevated HOMA2-IR suggest prediabetes and nutrition and lifestyle interventions are indicated
- ✓ Decreasing HOMA2-%B along with increasing HOMA2-IR suggests progression to type 2 diabetes.
- ✓ HOMA2-%B is not applicable for those taking exogenous insulin.[89]

In the initial stages of insulin resistance, where an increasing level of insulin is required to respond to blood glucose levels, the HOMA2-%B measurement will increase, representing the increased activity of the beta cells, and the increased insulin being secreted. Elevated HOMA2-%B measurements in addition to elevated HOMA2-IR measurements is indicative of prediabetes, and dietary and lifestyle intervention should be initiated.

After prolonged, untreated insulin resistance and overactivity of beta cells, the beta cells will lose their capacity to maintain an increased activity level, beta cell function and insulin production will decline, and this will be expressed by a decrease in the HOMA2-%B measurement. A decreasing HOMA2-%B measurement (decline of beta cell function and insulin secretion), in addition to an elevated HOMA2-IR measurement (rising level of insulin resistance) is indicative of progression to type 2 diabetes mellitus.

HOMA2-%S

- Standard range: 75-250%
- Optimal range: 85-200%

HOMA2-%S Summary

- ✓ Estimates insulin sensitivity, i.e., the capacity of peripheral cells to respond to insulin
- ✓ HOMA2-%S will be 100% in normal insulin sensitivity
- ✓ The higher the HOMA2-%S value, the more responsive cells are to insulin
- ✓ HOMA2-%S is linked to insulin resistance and should be accompanied by measurement of HOMA2-IR
- ✓ Decreases as insulin resistance increases

Decreased HOMA2-%S is indicative of decreasing levels of insulin sensitivity by the peripheral tissue cells. This is commonly seen in prediabetes and T2DM. Loss of Insulin sensitivity and decreased HOMA2-%S measures are secondary to chronically elevated insulin levels, which is usually a result of chronically elevated serum blood glucose levels.

A decreased HOMA2-%S measure would be seen in conjunction with an elevated HOMA2-IR measure, and an elevated HOMA2-%B measurement in the prediabetes, or perhaps early stages of T2DM, and would be seen in conjunction with a decreased HOMA2-%B measurement once the disease has progressed to the point of beta cell failure.

Quantitative Insulin Sensitivity Check Index (QUICKI)

QUICKI, a variation of HOMA, is a simple calculation that uses fasting glucose and fasting insulin to assess insulin sensitivity.

It was found to strongly correlate inversely with fasting insulin in those who were healthy nonobese nondiabetic; obese nondiabetic; and those with glucose intolerance or type 2 diabetes.[90]

QUICKI is the inverse of the sum of fasting insulin and fasting glucose logarithms [91]

QUICKI formula: 1 / [log(Fasting insulin in mIU/L) + log(Fasting glucose in mg/dL)]

A low value indicates insulin resistance[92]

- **Greater than 0.45** **Normal reference level**
- 0.30 - 0.45 Insulin resistance likely
- Less than 0.339 Associated with increasing insulin resistance, obesity, and cardiovascular risk
- Less than 0.30 Diabetes diagnosis likely

QUICKI was calculated and correlated with glucose clamp studies in non-obese, obese, and diabetic subjects: QUICKI decreased as insulin resistance increased:[93]

	Non-obese	Obese	Diabetic
Fasting glucose	83 mg/dL (4.6 mmol/L)	88 mg/dL (4.9 mmol/L)	161 mg/dL (8.9 mmol/L)
Fasting insulin	6 uU/mL (41.7 pmol/L)	16 uU/mL (111 pmol/L)	15 uU/mL (104 pmol/L)
QUICKI	0.38	0.33	0.30

A cohort study of 5511 adults suggests specific cutoff values for diagnosing metabolic syndrome and non-alcoholic fatty liver disease in men and women using QUICKI calculations.[94]

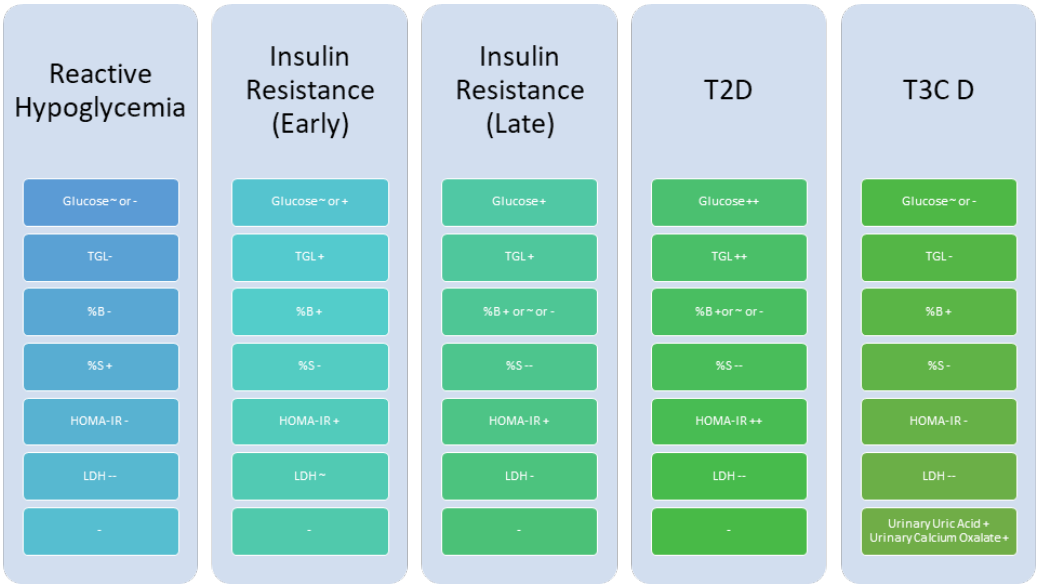
- Metabolic syndrome 0.343 in men and 0.331 in women
- NAFLD 0.347 in men and 0.333 in women

QUICKI:

- Standard Range 0.34 – 5
- Optimal Above 0.45

Characteristics of Dysglycemia

Interestingly, the HOMA2 tool is equally valuable for assessing and monitoring reactive hypoglycemia. In those instances, sensitivity will be increased, and beta cell function will be decreased. Moreover, when combined with a tool like a urinary sediment analysis, Type IIIc pancreatogenic dysglycemia and diabetes can also be assessed. Thank you to Dr. Brad Rachman for his valuable input below.



Source: Courtesy of Dr. Brad Rachman

How Far Down the Road to Diabetes is Someone?

A detailed assessment of an individual's risk factors, lifestyle, nutritional status, and blood chemistry profile will help pinpoint where they may be on the road to diabetes. Many of the risk factors for insulin resistance extend into the list of risk factors for T2DM.

Basic risk factors for type 2 diabetes (CDC)[95]

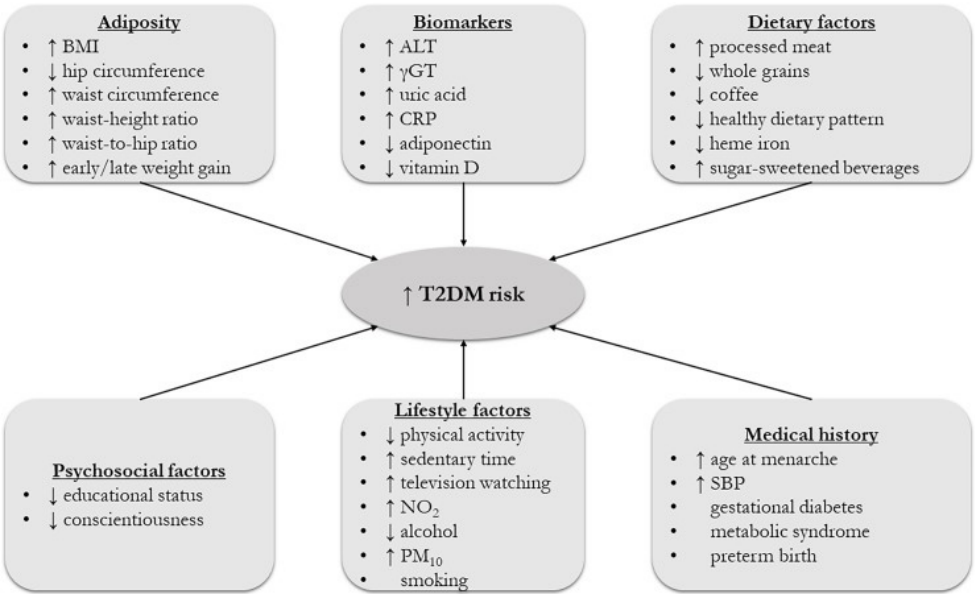
- 45 years old or older
- Ethnicity: African Americans, Hispanic, Native American, Native Alaskan
- Gestational diabetes
- Non-alcoholic fatty liver disease
- Overweight
- Parent, brother, or sister with T2DM
- Prediabetes
- Sedentary lifestyle (physically active fewer than 3 days/week)
- *[Note that CDC does not mention diet or nutrition as risk factors here.]*

A 2018 meta-analysis of 86 papers confirmed robust evidence for a variety of dietary, lifestyle, medical, biochemical, environmental, and psychosocial factors that increase risk of type 2 diabetes.[96]

- Adiposity, high BMI, metabolically unhealthy obesity, high waist circumference, high waist-to-height ratio, high waist-to-hip ratio, low hip circumference

- Decreased physical activity, high sedentary time and duration of television watching
- Low level of education and conscientiousness
- Smoking, air pollution
- Medical conditions
    - High systolic blood pressure, metabolic syndrome
    - Late menarche age, gestational diabetes, preterm birth
    - Major depressive disorder, bipolar disorder
    - Nitrogen dioxide exposure
    - Psoriasis
- Serum biomarkers
    - Increased alanine aminotransferase, gamma-glutamyl transferase, uric acid, ferritin, and C-reactive protein
    - Decreased level of adiponectin and vitamin D
- Unhealthy dietary pattern
    - Increased consumption of processed and red meat, sugar-sweetened beverages
    - Decreased intake of whole grains, coffee
    - Moderate intake of alcohol

Schematic representation of risk factors for T2DM with convincing or highly suggestive evidence



The symbol ↑ denotes a higher exposure to a risk factor, and the symbol ↓ represents a lower exposure to a risk factor. For alcohol consumption, never drinkers presented a higher risk for T2DM than moderate drinkers.

Source: Bellou, Vanesa et al. "Risk factors for type 2 diabetes mellitus: An exposure-wide umbrella review of meta-analyses." PloS one vol. 13,3 e0194127. 20 Mar. 2018, doi:10.1371/journal.pone.0194127 [R] This is an open access article distributed under the terms of the Creative Commons Attribution LIcense [R],

Patients traveling down this road may think that the prediabetes milepost is inconsequential. However, complications of prediabetes include heart disease and stroke and these complications extend in diabetes to kidney failure, blindness, and lower extremity amputation.[97]

What We Can Do To Reverse Insulin Resistance and the Risk of Diabetes

It is vitally important to identify blood glucose dysregulation before the pathology of diabetes sets in. Early assessment and intervention are indicated since insulin resistance is associated with abnormal lipid profiles and obesity as early as childhood and adolescence.[98]

In order to reverse insulin resistance, individuals must incorporate habits that are the opposite of habits that cause insulin resistance in the first place.

Diet and Insulin Resistance

Basically overeating, especially high-calorie, nutrient-deficient, highly processed foods and resultant obesity, promote insulin secretion and insulin resistance as well as metabolic syndrome, T2DM, and heart disease.

Overeating in general can promote insulin resistance though a variety of factors.

Insulin secretion following a meal will vary depending on meal content, gastrointestinal motility, gastric emptying, and hormonal and neural input following a meal. Ingestion of carbohydrate/glucose, fats/fatty acids, and protein/amino acids can ultimately stimulate insulin secretion.[99] [100] [101] [102]

Intake of animal fat, which is high in saturated fat, appears to be most closely associated with poor glycemic control and diabetes.[103]

Adoption of a Mediterranean diet was inversely correlated with insulin resistance in non-diabetics and actually reduced liver fat content in diabetics. Low meat intake in particular was associated with reduced prevalence of NAFLD.[104]

A Western-style diet that is highly processed and high in excess fat, animal fat, and processed carbohydrate foods can increase risk of insulin resistance, obesity, metabolic syndrome, and type 2 diabetes. However, severe restriction of carbohydrate is not necessarily beneficial as insulin is needed to help suppress endogenous glucose production, a significant factor in insulin resistance. *In fact, prolonged carbohydrate restriction can promote hepatic insulin resistance*.[105]

Modifying carbohydrate intake can help improve insulin resistance without going "too low." The RDA for carbohydrate is set at 130 grams/day to meet the brain's requirement for glucose. The central nervous system itself and red blood cells also require glucose for fuel.[106] Therefore, intake below 130 grams per day is considered "low carbohydrate." Intake between 130 grams and 225 grams per day would be considered moderate carbohydrate intake. Less than 30 grams per day would be considered a very low carbohydrate ketogenic diet (VLCKD), a level not recommended unless supervised and used for therapeutic purposes (e.g., epilepsy). [107]

- **Moderate carbohydrate:** 130 to 225g of carbohydrate/day
- **Low carbohydrate:** under 130g of carbohydrate/day
- **Very-low carbohydrate:** under 30g of carbohydrate/day

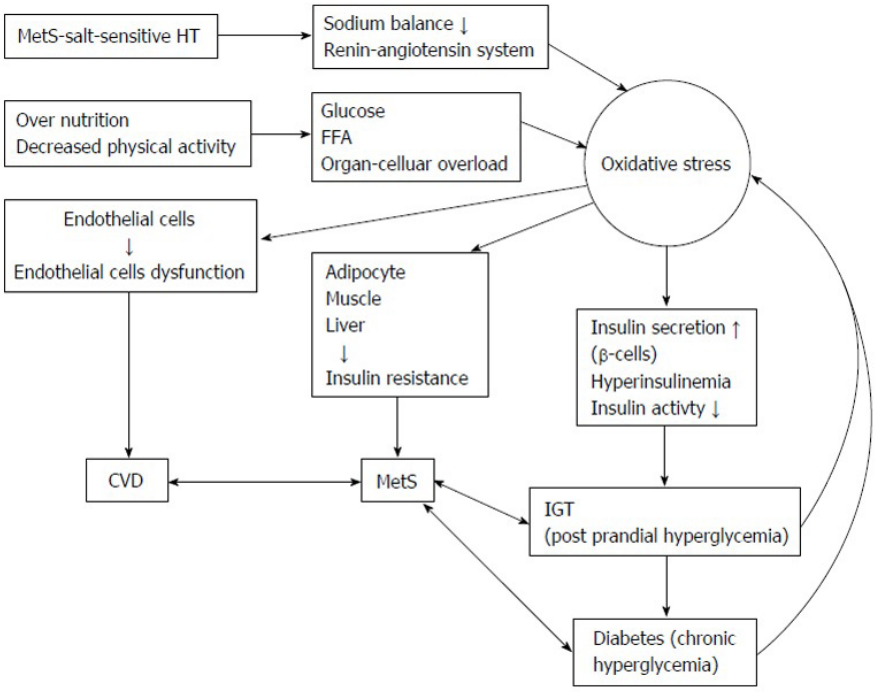
No doubt the typical Western diet is high in simple carbohydrates and concentrated sweets and beverages that offer no nutritional value and may contribute to nutrient depletion.

However, the Western diet is also acidogenic which promotes insulin resistance. Even subtle trends toward metabolic acidosis will produce insulin resistance, even in healthy individuals. Chronic metabolic acidosis (low serum bicarbonate, high anion gap, hypocitraturia, low urine pH) is associated with severe atherosclerosis, diabetes, cardiovascular disease, and chronic renal failure.[108]

Diet has a direct effect on acid-base balance and metabolic acidosis. Foods that increase production of acid in the body, at the biochemical level, include whole grains, meats, and eggs,

while fruits and vegetables are alkalizing and reduce acid load. Fats and sugars are considered neutral as is milk, which balances phosphorus content with buffering calcium.[109]

Fruits and vegetables also provide vital antioxidants that can help counteract oxidative stress, an underlying cause of beta cell dysfunction, insulin resistance, and T2DM. Reactive oxygen species that cause oxidative stress (in the absence of adequate antioxidants) can also contribute to insulin resistance at the tissue level and contribute to hypertension in salt sensitive individuals. Chronic oxidative stress also leads to oxidation of LDL cholesterol, atherosclerosis, CVD, increased sorbitol metabolism, and decreased glutathione generation in type 2 diabetes.[110]



Increasing reactive oxygen species in obesity, metabolic syndrome and salt sensitive hypertension. FFA: Free fatty acid; MetS: Metabolic syndrome; HT: Hypertension; IGT: Impaired glucose tolerance.

Physical Activity

A sedentary lifestyle is a significant risk factor for insulin resistance, obesity, and type 2 diabetes. It is also considered the fourth most significant risk factor contributing to mortality, accounting for 6% of deaths worldwide. HOMA values and inflammatory markers increased as sedentary (sitting) time increased in a cross-sectional study of 929 subjects.[111]

Exercise enhances glucose uptake and glycogen synthesis in skeletal muscle without the need for insulin. Even just six minutes of exercise prior to meals can improve glucose homeostasis throughout the day.[112]

Regular physical activity can improve insulin sensitivity and includes various forms of movement from house and garden tasks, to walking and cycling, to physically strenuous work and aerobic exercise. Even a single aerobic exercise session can improve insulin sensitivity by over 50% for up to 72 hours. However, these effects fade within 5 days without further exercise. Researchers estimate a reduction in T2DM risk with each 500 kcal per week increase in physical activity.[113]

Beyond improving insulin sensitivity, structured exercise can reduce visceral and subcutaneous

body fat, reduce body fat percentage, and promote weight loss, factors that can all reduce insulin resistance. Researchers note, however, that exercise without weight loss or improvements in body fat may not improve insulin resistance in the long term.[114]

A meta-analysis of 11 studies comprising 846 subjects demonstrated that regular exercise intervention in T2DM reduced fasting glucose, fasting insulin, HOMA-IR, hemoglobin A1C, and BMI. Research suggests that a combination of resistance training and aerobic activity (using large muscles, walking, cycling, jogging, swimming) for 150 minutes per week or more is most advantageous.[115]

Sleep

Adequate sleep is essential to glucose metabolism, and sleep deprivation can increase risk of obesity and diabetes. Inadequate sleep appears to negatively affect glucose homeostasis and contribute to insulin resistance because it is associated with :[116]

- ✓ Decreased beta cell responsiveness and insulin sensitivity
- ✓ Decreased leptin (the satiety "hormone") and increased ghrelin (the "hunger hormone"), leading to increased appetite and overeating
- ✓ Increased sympathetic nervous system activity and evening cortisol levels
- ✓ Disrupted sleep is independently associated with metabolic syndrome characteristics including insulin resistance, dyslipidemia, and elevated blood pressure
- ✓ Sleep disruption may be caused by sleep apnea which contributes to a vicious cycle of interrupted sleep, increased nervous system activation, glucose dysregulation, and obesity.
- ✓ A prospective study of more than 8000 adults found that disrupted sleep increased incident T2DM during a 7.5 year follow up period.
- ✓ Sleep duration is important. Sleeping for fewer than 6 or greater than 9 hours per night increased risk of T2DM in the Sleep Heart Health Study.

An Holistic Approach:

Education, Lifestyle, and Nutrition Are Key Factors

Not surprisingly, insulin resistance can be improved and even reversed with a healthy approach to weight reduction, calorie restriction, adequate sleep, and regular physical exercise.[117] [118] [119] Elevated blood pressure can also be improved with this approach.

One six-month program studied the effects of lifestyle education and modification on 160 individuals with prediabetes (fasting glucose 100-124 mg/dL 5.6-6.9 mmol/L). The study compared a one-time general review of lifestyle changes and prevention of type 2 diabetes to a more intensive structured program that incorporated education about prediabetes, diabetes, risk factors, and complications, diet improvements, and increased physical activity. Education was delivered in the form of lectures and workshops that took place at baseline and again 3 months into the study.[120] The more intensive interventions induced:

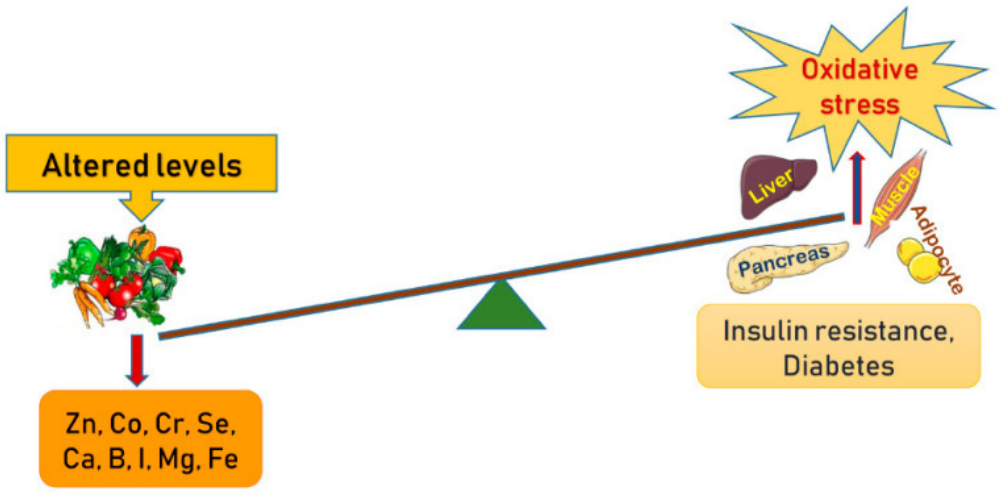
- Significant reductions in BMI, fasting glucose, insulin, HOMA-IR, hemoglobin A1C, and total carbohydrate intake; and
- Significantly increased fiber and micronutrient intake including vitamins A, C, E, B vitamins, calcium, magnesium, potassium, sodium, copper, iron, and phosphorus.

A healthy approach to weight maintenance and reduced risk of insulin resistance and diabetes will incorporate

- ✓ A Mediterranean plant-based diet centered around whole unprocessed foods
- ✓ Abundant intake of fresh fruits and vegetables (associated with lower diabetes incidence[121])
- ✓ Limited intake of animal-based fats
- ✓ Restricting or eliminating processed and canned foods
- ✓ Balanced macronutrients, adequate micronutrients
- ✓ Balanced glycemic load
- ✓ Weight loss of 7% reduced onset of T2DM by 58%[122]
- ✓ Incorporating physically active and structured exercise into one's daily routine

Micronutrients are especially important to metabolism, and minerals are especially at risk of becoming deficient in a highly processed diet. Minerals essential to glucose homeostasis, prevention of type 2 diabetes, and reduction of oxidative stress include:[123]

- Boron
- Calcium
- Chloride
- Chromium
- Cobalt
- Copper
- Iron
- Iodine
- Magnesium
- Molybdenum
- Phosphorous
- Potassium
- Sodium
- Sulfur
- Zinc



Schematic presentation of the altered levels of trace elements and minerals in the manifestation of oxidative stress in amplifying pathways towards insulin resistance and development of diabetes.

Source: Dubey, Pallavi et al. "Role of Minerals and Trace Elements in Diabetes and Insulin Resistance." Nutrients vol. 12,6 1864. 23 Jun. 2020, doi:10.3390/nu12061864 [R] This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license ([R]).

Chromium (trivalent chromium) is a trace element that is appears to be particularly important for glucose tolerance and insulin function.[124] Researchers note the importance of maintaining chromium sufficiency and recommend replacement in the event of insufficiency.[125] However, some researchers recommended more clinical trials before recommending chromium supplementation.[126]

Magnesium is especially important to glucose and insulin regulation, and research supports its use in insulin resistance. A meta-analysis of 12 studies supplementing with a range of magnesium from 250-450 mg per day demonstrated improvements in fasting glucose, fasting insulin, and HOMA-IR values.[127]

Other micronutrients that play an integral role in glucose homeostasis include vitamin E (tocopherols and tocotrienols), nicotinamide, B6, B12, folate, and vanadium.[128]

Sufficiency of vitamin D, thiamine, biotin, and vitamin C also appears to be associated with glucose homeostasis.[129]

Omega-3 fatty acids may also play an important role in mitigating insulin resistance and improving glucose metabolism due to their anti-inflammatory actions and support of mitochondrial function.[130]

Ideally adequate amounts of micronutrients can be obtained from the diet. However, if soil depletion, excessive processing, gastrointestinal disorders, or poor diet quality lead to insufficient micronutrient intake, then targeted supplementation may be indicated.

Optimal Takeaways

So, the bottom line is, insulin resistance and even prediabetes can be rerouted and reversed with nutrition and lifestyle changes. We just need the will and the way.

- ✓ Insulin resistance is a modifiable metabolic anomaly resulting primarily from an excess intake of calories, most often accompanied by insufficient micronutrient intake and sedentary lifestyle.
- ✓ Under normal circumstances insulin
    - Facilitates glucose transport into muscle
    - Increases glycogen synthesis and lipid storage
    - Suppresses gluconeogenesis, hepatic glucose production, and availability of fatty acids in circulation.
- ✓ As insulin resistance progresses, increasing amounts of insulin are needed to maintain glucose homeostasis, so blood glucose levels alone won't indicate what is going on under the surface.
    - It's important to measure fasting insulin and/or C-peptide, inflammatory markers, and other metabolic markers to get an accurate assessment of insulin resistance and T2DM risk.
    - HOMA2 and QUICKI can help identify insulin resistance and risk of type 2 diabetes
- ✓ Insulin resistance may not have symptoms in its early stages.
- ✓ As it advances, insulin resistance is associated with progressive glucose intolerance, inflammation, cardiovascular disease, hypertension, hypertriglyceridemia, non-alcoholic fatty liver disease, abdominal obesity, metabolic syndrome, and a significantly increased risk of type 2 diabetes.
- ✓ Insulin resistance can be improved or reversed with
    - Healthy weight loss if needed
    - Adoption of a balanced whole-foods based diet containing an abundance of fruits and vegetables, plant-based foods, herbs and spices, high quality protein, oily fish, healthy fats including omega-3 fats, and targeted supplementation as needed
    - Limited intake of animal-based fats, meats, and concentrated sweets
    - Incorporation of physical activity, regular exercise, and a healthy sleep pattern
- ✓ Education and motivation will be the keys to rerouting someone off the road to diabetes, and onto the highway to health and wellbeing.

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