Insulin Resistance and Diabetes

Type 2 diabetes mellitus (DM) begins with insulin resistance—cells become less sensitive to the effects of insulin and consequently cannot absorb enough glucose from the blood. Worsening insulin resistance eventually leads to prediabetes, and then to type 2 DM.

This newsletter will discuss insulin resistance and its relationship to prediabetes, type 2 DM, and other medical conditions ranging from cardiovascular to gynecologic. Also discussed are risk factors for insulin resistance, methods for diagnosis, and how lifestyle changes can treat insulin resistance and subsequently reduce the risk for developing diabetes.

Development of Insulin Resistance and Type 2 DM

Insulin resistance, rather than elevated fasting glucose or glycated hemoglobin (HbA_{1c}), is the earliest laboratory indicator of progression to type 2 DM. Insulin helps regulate blood glucose by stimulating glucose uptake by cells. In patients with insulin resistance, tissues do not respond fully to the effects of insulin. To compensate, pancreatic beta cells produce greater amounts of insulin to maintain a normal blood glucose level. Eventually, insulin resistance may become so severe that the beta cells can no longer produce enough insulin to compensate.[1] When this happens, blood glucose rises to levels defining prediabetes (100 mg/dL to 125 mg/dL) and ultimately type 2 DM (≥126 mg/dL).[2] This progression from insulin resistance to onset of type 2 DM is believed to take 10 to 15 years.[3]

Scope of the Problem

The scope of the problem is enormous. More than 60 million people in the United States are estimated to have insulin resistance,[4] 84 million have prediabetes, and 30 million (9% of the population) have diabetes, with type 2 DM accounting for 90% to 95% of all cases.[5]

Causes and Associated Medical Conditions

Insulin resistance is primarily caused by excess body fat.[1] Excess insulin results in weight gain in the form of fat, which further exacerbates resistance to insulin.[1]

Metabolic syndrome is considered an indicator of insulin resistance.[3] Medical conditions associated with insulin resistance include cardiovascular disease, nonalcoholic fatty liver disease (NAFLD), polycystic ovarian syndrome (PCOS), Alzheimer disease, and cancer.[1] Because insulin resistance precedes diabetes, it is also associated with the microvascular complications of diabetes (neuropathy, retinopathy, and nephropathy).

Risk Factors

Risk factors for insulin resistance are the same as those for the development of type 2 DM[2]:

- Age: ≥ 45 years
- Race/ethnicity: African American, Hispanic/Latino American, Native American, Pacific Islander, or Asian American
- Physically inactive: <10 minutes per week of moderate or vigorous activity

Signs a Patient May Have Insulin Resistance

Findings on history and physical examination that should raise the suspicion of insulin resistance include[3,6]

- Obesity, hypertension, or hyperlipidemia
- Increased waist circumference (for sex/race)
- Metabolic syndrome
- Prediabetes
- Microvascular disease (retinopathy, neuropathy, nephropathy)
- Macrovascular disease (stroke, coronary or peripheral artery disease)
- PCOS
- Characteristics of PCOS (menstrual irregularities, hirsutism, acne, and alopecia)
- Xanthelasma or xanthomas
- Acanthosis nigricans
- Findings consistent with type A or type B insulin resistance syndrome

- Overweight or obese (BMI ≥25 kg/m^2 or ≥23 kg/m^2 in Asian Americans)
- High blood pressure: ≥140/90 mm Hg
- Low level of high-density lipoprotein (HDL) cholesterol: <35 mg/dL
- High level of triglycerides: >250 mg/dL
- Family history: first-degree relative with diabetes
- Personal history: cardiovascular disease, women with gestational diabetes or PCOS
- Prior testing: HbA$_{1c}$ ≥5.7%, impaired glucose tolerance, or impaired fasting glucose

Diagnosis of Insulin Resistance

Insulin resistance has no typical signs or symptoms, and at an early stage blood glucose and HbA$_{1c}$ may be normal. As such, it is difficult to diagnose. A thorough history and physical examination are important, as they can identify risk factors and clinical signs (see Sidebar on previous page).

Methods to directly measure insulin resistance include the hyperinsulinemic-euglycemic glucose clamp technique and the insulin suppression test.[7] These methods, however, have limited use in a routine clinical setting due to the technical requirements and time required to perform the tests. Other methods, while useful, have drawbacks. Either they do not identify insulin resistance at an early stage, use surrogate markers for insulin resistance, or are also cumbersome to perform.[7] Recently, Quest Diagnostics reported a simple approach that uses serum measurements of fasting insulin and C-peptide, co-secreted with insulin by pancreatic beta cells, to measure insulin resistance.[8]

Treating Insulin Resistance

Lifestyle interventions can prevent or delay the progression of insulin resistance to type 2 DM.[9] Individuals can reduce caloric intake, especially carbohydrates, which stimulate excessive insulin demand. They can also increase physical activity, which increases energy expenditure and improves muscle insulin sensitivity. The National Diabetes Prevention Program certifies lifestyle-change programs around the country.[9] Participants can take classes in person or online. Classes cover topics such as eating healthy, increasing physical activity, and setting goals and staying motivated.

How the Laboratory Can Help

Quest Diagnostics offers tests that can help identify individuals with insulin resistance, diagnose prediabetes, and estimate the risk for developing type 2 DM. The Cardio IQ® Insulin Resistance Panel with Score (test code 36509) assesses the likelihood of insulin resistance. The Cardio IQ Diabetes Risk Panel with Score (test code 92026) is used to help diagnose prediabetes, assess risk for developing type 2 DM, and identify individuals who may benefit from lifestyle changes and/or medical treatment.

For more information see:

- The Cardio IQ Insulin Resistance Panel with Score: QuestDiagnostics.com/testcenter/testguide.action?dc=TS_CardioIQ_IR
- General Diabetes Testing Services: QuestDiagnostics.com/home/physicians/testing-services/condition/diabetes

References

1. Fung J, Berger A. Hyperinsulinemia and insulin resistance: scope of the problem. *J Insulin Resist.* 2016;1:a18.

2. Standards of medical care in diabetes —2017. American Diabetes Association website. https://professional.diabetes.org/sites/professional.diabetes.org/files/media/standardofcare2017fulldeckfinal_0.pdf. Accessed September 4, 2018.

3. Freeman AM, Pennings N. Insulin resistance. *StatPearls [Internet].* Treasure Island, FL: StatPearls Publishing; 2018. https://www.ncbi.nlm.nih.gov/books/NBK507839/. Updated June 26, 2018. Accessed September 1, 2018.

4. About diabetes. American Heart Association website. https://www.heart.org/en/health-topics/diabetes/about-diabetes. Accessed October 1, 2018.

5. National diabetes statistics report, 2017. Centers for Disease Control and Prevention website. http://www.diabetes.org/assets/pdfs/basics/cdc-statistics-report-2017.pdf. Accessed September 1, 2018.

6. Tritos NA, Mantzoros CS. Syndromes of severe insulin resistance. *J Clin Endocrinol Metabol.* 1998;83:3025-3030.

7. Muniyappa R, Lee S, Chen H, et al. Current approaches for assessing insulin sensitivity and resistance in vivo: advantages, limitations, and appropriate usage. *Am J Physiol Endocrinol Metab.* 2008;294:E15-E26.

8. Abbasi F, Shiffman D, Tong CH, et al. Insulin resistance probability scores for apparently healthy individuals. *J Endocr Soc.* 2018;2:1050-1057.

9. National Diabetes Prevention Program. Centers for Disease Control and Prevention website. https://www.cdc.gov/diabetes/prevention/index.html. Updated August 10, 2018. Accessed September 6, 2018.