## Insulin Resistance and the Evolution of Type 2 Diabetes

Type 2 diabetes mellitus (DM) generally evolves from a state of insulin resistance—cells become less sensitive to the effects of insulin—and consequently cannot regulate blood glucose levels appropriately.[1-3] Worsening insulin resistance eventually leads to prediabetes, and then to type 2 DM.[1-3]

This article reviews how insulin resistance contributes to the evolution of type 2 DM, a global health issue. Risk factors and laboratory testing that help identify individuals with insulin resistance are discussed, as well as lifestyle changes that can treat or prevent the development of DM and reduce the risk of other serious conditions associated with insulin resistance. Also reviewed are DM screening recommendations, diagnosis, management, complications, and comorbidities.

### Type 2 DM: A Global Health Issue

The World Health Organization estimates that, worldwide, approximately 422 million people have diabetes.[4] The Centers for Disease Control and Prevention estimates that 34 million people in the United States have diabetes, and 1 in 5 do not know they have it.[5] Notably, more than 88 million adults in the United States have prediabetes, and 84% do not know they have it.[5] Diabetes is the seventh leading cause of death in the United States; in the past 2 decades, the number of adults with diabetes has more than doubled owing to the aging population and the increase in the number of people who are overweight or obese.[5]

### Insulin Resistance: A Metabolic Condition

Insulin resistance, rather than elevated fasting glucose or glycated hemoglobin (HbA1c), is the earliest laboratory indicator of progression to type 2 DM.[1,2,6] Insulin regulates fasting blood glucose levels by regulating the formation and release of glucose by the liver and 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 fasting blood glucose level. Eventually, insulin resistance may become so severe that the beta cells can no longer produce enough insulin to compensate.[1,2,6] When this happens, fasting blood glucose rises from normal levels to levels defining prediabetes and ultimately type 2 DM.[7] This progression from insulin resistance to onset of type 2 DM is believed to take 10 to 15 years.[2] The combination of insulin resistance and compensatory hyperinsulinemia can result in the "metabolic syndrome," which is defined by a cluster of abnormalities including obesity, hypertension, dyslipidemia, type 2 DM, and cardiovascular diseases (CVD) such as atherosclerotic heart disease.[1]

#### *Identifying Insulin Resistance*

Insulin resistance has no typical signs or symptoms, and at an early stage blood glucose and HbA1c may be normal (fasting glucose 99 mg/dL; HbA1c <5.7%).[2] As such, it is difficult to diagnose. However, certain signs should raise the suspicion of insulin resistance[2,8]:

- Obesity, hypertension, or hyperlipidemia
- Increased waist circumference (for gender/race)
- Metabolic syndrome
- Prediabetes
- Microvascular disease (retinopathy, neuropathy, nephropathy)
- Macrovascular disease (stroke, coronary or peripheral artery disease)
- Polycystic ovary syndrome (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

#### *Laboratory Testing*

Methods to directly measure insulin resistance include the hyperinsulinemic-euglycemic glucose clamp technique and the insulin suppression test.[9] 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, using surrogate markers for insulin resistance have drawbacks such as not identifying insulin resistance at an early stage, and being cumbersome to perform.[9] Consequently, measurement of insulin resistance using these methods is not currently recommended in guidelines for DM[7,10] or PCOS.[11]

However, recent studies using surrogate markers of insulin resistance have shown promise for assessing the risk of prediabetes. For example, the combination of HbA1c and Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) score, a surrogate marker that uses fasting insulin and glucose levels, improved risk assessment for type 2 DM as compared to HbA1c alone.[12]

A simpler surrogate marker based on simultaneous serum measurements of fasting insulin and C-peptide in a single tandem mass spectrometry assay was recently described.[13] Using an insulin resistance score (IRScore) based on these measurements, the risk of type 2 DM was assessed in a population of older Europeans.[14] Being in the top versus the bottom tertile of the IRScore was associated with incident type 2 DM after adjusting for established risk factors, except for prediabetes status (hazard ratio [HR] 2.1, 95% confidence interval [CI]: 1.7–2.5; *P*< .0001).[14]

#### *Treating Insulin Resistance*

Lifestyle interventions can prevent or delay the progression of insulin resistance to type 2 DM.[7,15] 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.[15] Participants can take classes in person or online. Classes cover topics such as eating healthy, increasing physical activity, and setting goals and staying motivated.

#### *Serious Conditions Associated With Insulin Resistance*

Insulin resistance is associated with serious cardiometabolic diseases including CVD, chronic kidney disease (CKD), and nonalcoholic fatty liver disease (NAFLD) (see Sidebar).

### Screening, Diagnosis, Management, and Complications of Type 2 DM

#### *American Diabetes Association Recommendations*

The American Diabetes Association (ADA) recommends that individuals without risk factors begin testing for prediabetes/diabetes when they are 45 years old.[7] They also recommend testing for type 2 DM and prediabetes in asymptomatic people who are overweight or obese (BMI ≥25 kg/m$^2$ or ≥23 kg/m$^2$ in Asian Americans) who have 1 or more of the following risk factors[7]:

- 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
- 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: CVD, women with gestational diabetes or PCOS
- Prior testing: HbA1c ≥5.7%, impaired glucose tolerance, or impaired fasting glucose

The diagnosis of DM or prediabetes is based on 1 or more of the following laboratory test results[7]:

- Fasting plasma glucose (FPG ≥126 mg/dL, diabetes; 100-125 mg/dL, prediabetes)
- Plasma glucose after a 75-g oral glucose load (2-hour PG ≥200 mg/dL, diabetes; 140-199 mg/dL, prediabetes)
- Hemoglobin A1c (HbA1c ≥6.5%, diabetes; 5.7% to 6.4%, prediabetes)

#### *United States Preventive Services Task Force Screening Recommendations*

The United States Preventive Services Task Force (USPSTF) recently updated their recommendations for screening for prediabetes and diabetes.[16] The USPSTF now recommends screening for prediabetes and type 2 DM in adults 35 to 70 years of age who are overweight (BMI ≥25 kg/m$^2$) or obese (BMI ≥30 kg/m$^2$). They also recommend that clinicians offer or refer patients with prediabetes to effective preventive interventions.

#### *Treatment Goals*

For patients with DM, recommended glucose targets are not stringent and may be modified by factors such as patient age, life expectancy, comorbid conditions, and complications.[7] In general, recommended values are a preprandial glucose of 70 mg/dL to 130 mg/dL, peak postprandial glucose of <180 mg/dL, and HbA1c of <7%.[7]

Around half of patients with type 2 DM do not meet glucose management goals. A major reason is poor medication adherence, which may be caused by lack of perception and knowledge of DM, concern about treatment side effects, low expectations regarding treatment (eg, perceived treatment inefficacy), high medication cost, high complexity of the treatment regimen, and lack of a support system.[3,25-27]

#### *Management*

Healthcare providers can help patients meet glucose management goals through education about DM and risk factors for developing complications. Referring patients with prediabetes to a prevention program can decrease the chance they will develop DM by up to 58% (The National Diabetes Prevention Program: CDC.gov/Diabetes/Prevention/Index.html). DM management programs (CDC.gov/LearnMoreFeelBetter/Programs/Diabetes.htm), especially those with a high degree of patient contact and disease education, can also increase adherence to treatments.[3,25,26]

#### *Complications and Comorbidities*

Untreated diabetes can lead to serious complications, including peripheral arterial disease and potential amputation, blindness (macular retinopathy), and renal failure. As for insulin resistance, DM also has a strong association with cardiometabolic comorbidities (see Sidebar). However, effective management of elevated glucose levels and lifestyle modifications can reduce the risk of these adverse outcomes.[7,10]


**References**

1. Sattar N, Welsh P, Pressa D. The insulin resistance syndrome. In: DeFronzo RA, Ferrannini E, Zimmet P, et al, eds. *International Textbook of Diabetes Mellitus*. 4th ed. Wiley-Blackwell; 2015:337-353. doi:10.1002/9781118387658.ch23
2. Petersen MC, Shulman GI. Mechanisms of insulin action and insulin resistance. *Physiol Rev*. 2018;98(4):2133-2223. doi:10.1152/physrev.00063.2017
3. Freeman AM, Pennings N. Insulin resistance. In: *StatPearls [Internet]*. StatPearls Publishing; 2021. Updated July 10, 2021. Accessed September 9, 2021. https://www.ncbi.nlm.nih.gov/books/NBK507839/
4. Diabetes: key facts. World Health Organization. Published April 13, 2021. Accessed September 9, 2021. https://www.who.int/news-room/fact-sheets/detail/diabetes
5. Diabetes fast facts. Centers for Disease Control and Prevention. Reviewed June 11, 2020. Accessed September 9, 2021. https://www.cdc.gov/diabetes/basics/quick-facts.html
6. da Silva Rosa SC, Nayak N, Caymo AM, et al. Mechanisms of muscle insulin resistance and the cross-talk with liver and adipose tissue. *Physiol Rep*. 2020;8(19):e14607. doi:10.14814/phy2.14607
7. American Diabetes Association. Standards of medical care in diabetes—2021. *Diabetes Care*. 2021;44(suppl 1):S1-S232.
8. Trifos NA, Mantzoros CS. Clinical review 97: syndromes of severe insulin resistance. *J Clin Endocrinol Metabol*. 1998;83(9):3025-3030. doi:10.1210/jcem.83.9.5143
9. 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(1):E15-E26. doi:10.1152/ajpendo.00645.2007
10. US Preventive Services Task Force. Screening for prediabetes and type 2 diabetes: US Preventive Services Task Force Recommendation Statement. *JAMA*. 2021;326(8):736-743. doi:10.1001/jama.2021.12531
11. Goodman NF, Cobin RH, Futterweit W, et al; American Association of Clinical Endocrinologists, American College of Endocrinology, and Androgen Excess and PCOS Society Disease State Clinical Review: guide to the best practices in the evaluation and treatment of polycystic ovary syndrome-part 2. *Endocr Pract*. 2015;21(12):1415-1426. doi:10.4158/EP15748.DSCPT2
12. Mingis JB, Pomeaba B, Leong A, et al. Simultaneous consideration of HbA1c and insulin resistance improves risk assessment in white individuals at increased risk for future type 2 diabetes. *Diabetes Care*. 2020;43(8):e90-e92. doi:10.2337/dc20-0716
13. Abbasi F, Shiffman D, Tong CH, et al. Insulin resistance probability scores for apparently healthy individuals. *J Endocr Soc*. 2018;2(9):1050-1057. doi:10.1210/js.2018-00107
14. Shiffman D, Louie JZ, Mingis JB, et al. An insulin resistance score improved diabetes risk assessment in the Malmö Prevention Project:a longitudinal population-based study of older Europeans. *Diabetes Care*. 2021;44(2):E28. doi:10.2337/dc21-1528
15. Lifestyle change program providers. Centers for Disease Control and Prevention. Reviewed August 3, 2021. Accessed October 8, 2021. https://www.cdc.gov/diabetes/prevention/program-providers.htm
16. Kosmas CE, Silverio D, Tsomtou C, et al. The impact of insulin resistance and chronic kidney disease on inflammation and cardiovascular disease. *Clin Med Insights Endocrinol Diabetes*. 2018;11:1179551418792257. doi:10.1177/1179551418792257
17. Schmidt AM. Diabetes mellitus and cardiovascular disease. *Arterioscler Thromb Vasc Biol*. 2019;39(4):558-568. doi:10.1161/ATVBAHA.119.310961
18. Whaley-Connell A, Sowers JR. Insulin resistance in kidney disease: is there a distinct role separate from that of diabetes or obesity? *Cardiorenal Med*. 2017;8(1):41-49. doi:10.1159/000479801
19. Chen TK, Knicely DH, Grams ME. Chronic kidney disease diagnosis and management: a review. *JAMA*. 2019;322(13):1294-1304. doi:10.1001/jama.2019.14745
20. Kitade H, Chen G, Ni Y, et al. Nonalcoholic fatty liver disease and insulin resistance: new insights and potential new treatments. *Nutrients*. 2017;9(4):387. doi:10.3390/nu9040387
21. Bril F, McPhaul MJ, Kalavalapalli S, et al. Intact fasting insulin identifies nonalcoholic fatty liver disease in patients without diabetes. *J Clin Endocrinol Metab*. 2021;dgab417. doi:10.1210/clinem/dgab417
22. Fujii H, Kawada N; Japan Study Group of NAFLD (JSG-NAFLD). The role of insulin resistance and diabetes in nonalcoholic fatty liver disease. *Int J Mol Sci*. 2020;21(11):3863. doi:10.3390/ijms21113863
23. Dewidar B, Kahl S, Pafili K, et al. Metabolic liver disease in diabetes - from mechanisms to clinical trials. *Metabolism*. 2020;111(suppl):154299. doi:10.1016/j.metabol.2020.154299
24. Budd J, Cusi K. Role of agents for the treatment of diabetes in the management of nonalcoholic fatty liver disease. *Curr Diab Rep*. 2020;20(11):59. doi:10.1007/s11892-020-01349-1
25. About diabetes. American Heart Association. Reviewed May 4, 2021. Accessed September 13, 2021. https://www.heart.org/en/health-topics/diabetes/about-diabetes
26. National diabetes statistics report, 2020. Centers for Disease Control and Prevention. Accessed September 13, 2021. https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf
27. Guero B, Chanan N, Kaur S, et al. Lack of treatment persistence and treatment nonadherence as barriers to glycaemic control in patients with type 2 diabetes. *Diabetes Ther*. 2019;10(2):437-449. doi:10.1007/s13300-019-0590-x


Content reviewed 11/2021

### Insulin Resistance, Diabetes, and Associations With Cardiometabolic Diseases

Insulin resistance and diabetes are associated with increased risk of cardiometabolic diseases— interrelated disorders that affect cardiovascular and metabolic health. Examples include

*CVD*

- Insulin resistance is associated with an increased risk of CVD, even in persons who do not have diabetes.[16]
- CVD is a leading cause of morbidity and mortality in persons with type 2 DM.[16]
- Individuals with DM and manifestations of CVD (eg, myocardial infarction) have a mortality risk that is almost twice that of persons without DM.[17]

*CKD*

- Insulin resistance is associated with an increased risk of CKD.[18] The increased risk is independent of the increased risk associated with DM.[18]
- CKD has been considered an "insulin-resistant state," and even early-stage CKD is associated with a 40% to 100% increased risk of CVD.[18]
- In addition to optimal glucose control, management and risk reduction for individuals with CKD include CVD risk reduction (eg, statins and blood pressure control), treatment of albuminuria, and avoidance of potential nephrotoxins.[19]

*NAFLD*

- NAFLD is the result of insulin resistance and excessive fatty acids in the circulation.[20] It is a chronic condition that is characterized by fat accumulation and/or inflammation in the liver and progresses from simple hepatic steatosis (nonalcoholic fatty liver [NAFL]), to nonalcoholic steatohepatitis (NASH), and ultimately to cirrhosis.[20]
- Persons with NAFLD have higher fasting intact insulin levels regardless of diabetes status (type 2 DM or no type 2 DM).[21]
- NAFLD is associated with fibrosis, cirrhosis, hepatocellular carcinoma, CVD, and increased cardiovascular and liver-related mortality.[22,23]
- Although, NAFLD is not "curable," lifestyle modifications and certain drugs can reduce, and in some cases, reverse progression.[24,25]

### How the Laboratory Can Help

Quest Diagnostics offers tests that can help identify patients with insulin resistance and diagnose prediabetes and diabetes. Tests are also available that can help estimate the risk for developing type 2 DM and complications of diabetes, and also identify patients who may benefit from lifestyle changes and/or medical treatment. Quest also offers test panels that include risk scores that may assist providers in communicating risk in terms that patients will better understand.

For more information visit QuestDiagnostics.com/Home/Physicians/Testing-Services/Condition/Diabetes/.