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Evaluation and Intervention Methods for Patients with Prediabetes of Different Phenotypes

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Abstract: Prediabetes is a heterogeneous condition, encompassing various pathological phenotypes such as hyperinsulinemia, tissue-specific insulin resistance (IR), systemic IR, and β-cell dysfunction. A significant proportion of individuals with prediabetes remain undiagnosed. Furthermore, although lifestyle interventions have demonstrated efficacy in improving prediabetic conditions, some individuals with prediabetes progress to type 2 diabetes mellitus. This study aims to summarize effective evaluation methods for identifying distinct pathological phenotypes of prediabetes and targeted lifestyle intervention strategies to mitigate the progression from prediabetes to diabetes.

Keywords: Prediabetes; Type 2 diabetes mellitus; Evaluation methods; Lifestyle intervention

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1. Introduction

Type 2 diabetes mellitus (T2DM) affects approximately 508 million people worldwide, posing significant medical, social, and economic challenges [1]. Previous studies have demonstrated that T2DM exhibits multiple pathological phenotypes and developmental trajectories, which arise from diverse underlying causes [2]. Proper assessment of these distinct phenotypes and implementation of tailored interventions are crucial for effective disease management.

However, research indicates that 90% of individuals with prediabetes remain undiagnosed [3]. Moreover, current lifestyle interventions for prediabetes are goal-based, providing uniform weight loss and physical activity targets for all participants. This approach results in a subset of individuals adhering to lifestyle modifications without experiencing improvement in their condition. Thus, this study seeks to summarize the evaluation methods for different pathological phenotypes in the progression of prediabetes to T2DM and propose targeted lifestyle

interventions to address this variability effectively.

2. Evaluation for the pathological phenotype of prediabetes

Determining the pathological phenotype of prediabetic patients is a fundamental step in designing individualized intervention programs. The hyperinsulinemic-euglycemic clamp is considered the gold standard for measuring systemic insulin resistance (IR) [4]. When combined with radiolabeled glucose or free fatty acids (FFA), it can quantify the contribution of hepatic [5], muscular [6], or adipose IR [7]. However, this method is time-intensive, technically complex, and unsuitable for general clinical practice or large-scale epidemiological studies. Consequently, various surrogate markers have been developed in recent years to assess IR and β-cell function.

3. Evaluation of hyperinsulinemia

To sustain life under fasting conditions, circulating insulin levels should range from approximately 25 to 70 pmol/L (25th–75th percentile) [8]. Depending on dietary carbohydrate content, insulin levels can rise to approximately 300–800 pmol/L [9,10]. Hyperinsulinemia is diagnosed when fasting insulin levels are ≥ 15 mU/mL and/or insulin peaks reach ≥ 150 mU/mL after an oral glucose tolerance test (OGTT) [11]. However, research indicates that hemolyzed blood samples, commonly seen in fasting trials, can lead to underestimation of insulin levels and reduced diagnostic performance. A C-peptide level of 0.3 nmol/L concurrent with hypoglycemia (< 2.3 mmol/L) appears to be the most reliable criterion for diagnosing endogenous hyperinsulinism [12].

4. Evaluation of tissue-specific and systemic insulin resistance

IR is characterized by impaired insulin action, resulting in decreased glucose uptake by muscles, increased hepatic glucose production (HGP), and enhanced lipolysis in adipose tissue [13]. Following overnight fasting, the liver accounts for over 90% of endogenous glucose production (EGP) [14]. Since plasma insulin strongly inhibits EGP, the product of fasting plasma insulin (FPI) and fasting blood glucose (FPG) levels can indicate the extent of hepatic IR [15]. The glucose level two hours after an OGTT reflects the ability of peripheral tissues, particularly skeletal muscles, to dispose of glucose [16] and is used to evaluate muscle IR. The adipose tissue insulin resistance index (Adipo-IR), calculated by multiplying fasting FFA and FPI concentrations, measures adipose IR [17-19].

The relationship between insulin and glucose levels during OGTT provides a more robust indicator of hepatic and muscle IR than isolated plasma insulin or glucose measurements [6]. During the initial 0–30 minutes of OGTT, plasma glucose concentration rises, stimulating insulin secretion by β-cells. Hyperglycemia combined with hyperinsulinism inhibits EGP, primarily during this phase [20]. Thus, the product of glucose and insulin area under the curve (AUC) during the 0–30-minute period [$glucose_{0–30min}$(AUC) × $insulin_{0–30min}$(AUC)] assesses hepatic IR [21,22]. This approach considers both fasting and post-load liver function. The rate of plasma glucose decline from the peak (~60 minutes) to the nadir reflects peripheral glucose uptake (mainly by muscles) and the insulin response to hyperglycemia. The muscle insulin sensitivity index (MISI) is calculated as the rate of glucose concentration decline divided by plasma insulin concentration (dG/dt ÷ I) [21-23]. However, this method is unsuitable for type 2 diabetes mellitus (T2DM) patients, where blood glucose levels often continue to rise during the 60–120-minute period of OGTT.

For systemic IR or sensitivity assessment, commonly used indicators include HOMA-IR (FPI × FPG / 22.5) [24] and ISI-Matsuda (10,000 / √[FPG × FPI × mean glucose × mean insulin during OGTT]) [25].

5. Evaluation of β-cell dysfunction

β-cells respond to increases in blood glucose (ΔG) by secreting insulin (ΔI) [9]. The insulin production index is calculated as the ratio of insulin increase to glucose increase (ΔI/ΔG) during the 0–30-minute OGTT phase. β-cells can also adjust insulin secretion in response to changes in insulin sensitivity to maintain normoglycemia [26,27]. The Disposition Index (DI), considered the gold standard for assessing β-cell function, is calculated as the insulin production index × ISI-Matsuda or the insulin production index / HOMA-IR [28]. Additionally, HOMA-β is another reliable measure of β-cell function [29], calculated as 20 × FPI / (FPG – 3.5) [24].

6. Interventions for prediabetes

Current lifestyle interventions for individuals with prediabetes are primarily goal-based, where participants are provided with uniform weight loss and physical activity targets. However, no studies have yet established how to tailor interventions effectively for patients with distinct prediabetic phenotypes. Consequently, a significant proportion of individuals with prediabetes progress to T2DM [30]. Targeted interventions based on specific metabolic phenotypes and the primary tissues involved in IR may provide a more effective strategy to reduce the risk of T2DM [31]. Since β-cell dysfunction results from overnutrition and/or IR, alleviating hyperinsulinemia and/or IR caused by overnutrition can naturally mitigate β-cell dysfunction. This section highlights intervention strategies aimed at improving hyperinsulinemia and tissue-specific IR.

7. Improving hyperinsulinemia

One direct approach to reducing circulating insulin levels is to limit pancreatic β-cell exposure to insulin secretagogues [10], particularly dietary carbohydrates, as they are a primary driver of insulin secretion [32,33]. Calorie restriction (CR) is a widely adopted method for reducing β-cell stimulation. Standard CR protocols involve a reduction of daily energy intake by 20% to 50% [34]. Studies have demonstrated that 6–12 weeks of CR can reduce fasting insulin levels in individuals with prediabetes by 11% to 41% [34-37]. However, due to poor adherence, long-term success rates of continuous CR or traditional CR are low. To address this, intermittent fasting (IF) has emerged as an alternative dietary strategy.

IF can be categorized into four primary methods: alternate-day fasting (ADF), alternate-day modified fasting (ADMF), 5:2 intermittent fasting (5:2 IF), and time-restricted feeding (TRF). Research shows that IF can effectively reduce fasting insulin levels in prediabetic individuals, achieving results comparable to those of CR [34]. For instance, a 10-week intervention combining calorie restriction or a liquid diet significantly reduced insulin levels in obese women. Similarly, limiting eating windows to fewer than six hours daily over five weeks markedly reduced insulin levels in men with prediabetes.

8. Improving tissue-specific insulin resistance

Evidence indicates that different metabolic tissues respond variably to interventions aimed at enhancing insulin sensitivity. A very low-calorie diet (VLCD) has shown effectiveness in improving hepatic glucose metabolism, reducing liver steatosis, and alleviating hepatic IR, but it has little impact on insulin-stimulated peripheral glucose

uptake or intramuscular lipid content. Additionally, TRF has demonstrated greater efficacy in improving hepatic IR compared to muscle IR, likely because the liver clock adapts more quickly to new dietary conditions than the muscle clock [31].

As skeletal muscle is directly influenced by physical activity, exercise is particularly effective for improving muscle IR. In cases where prediabetes is associated with muscle IR, exercise should be prioritized as a treatment. Both aerobic and resistance exercise have been shown to enhance muscle insulin sensitivity, despite differences in their molecular mechanisms. Dietary strategies such as the Mediterranean diet (MD) and the Paleolithic diet have also demonstrated effectiveness in improving peripheral insulin sensitivity.

Exercise significantly impacts adipose tissue by reducing fat cell size, decreasing lipid content, and enhancing glucose transport and metabolism in adipose cells through repeated activation of lipolysis. Dietary interventions to improve adipose tissue health include modifying diet composition, restricting eating windows, and consuming specific food types. For instance, low-carbohydrate (LCD), low-fat (LFD), ketogenic (KD), and high-protein (HPD) diets have shown potential benefits for treating obesity. However, their impact on lipid metabolism requires further investigation. Studies in db/db mice have shown that CR for three weeks increased GLUT4 protein levels in adipose tissue, indicating that CR may improve adipose IR.

A plant-based diet (PBD) is also associated with benefits for adipose tissue IR due to its lower content of total fat, saturated fat, cholesterol, and energy, combined with higher levels of unsaturated fatty acids and dietary fiber. Increasing the ratio of unsaturated to saturated fatty acids is critical for improving adipose IR, suggesting that PBDs may effectively enhance adipose tissue function and insulin sensitivity.

9. Conclusion

The development of distinct phenotypes of prediabetes is influenced by multiple factors, including genetics, diet, and environmental conditions. Assessing the pathological characteristics and phenotypes of patients using various methods is a fundamental prerequisite for effective intervention and treatment. Different dietary and exercise regimens yield varying effects on hyperinsulinemia and tissue-specific IR. To optimize outcomes, patients with prediabetes should adopt more personalized lifestyle interventions tailored to their specific metabolic profiles and phenotypic characteristics.

Author contributions

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Disclosure statement

The authors declare no conflict of interest.

References

[1] GBD 2021 Diabetes Collaborators, 2023, Global, Regional, and National Burden of Diabetes from 1990 to 2021, with Projections of Prevalence to 2050: A Systematic Analysis for the Global Burden of Disease Study 2021. Lancet, 402(10397): 203–234. https://doi.org/10.1016/S0140-6736(23)01301-6. Erratum in Lancet, 402(10408): 1132. https://doi.org/10.1016/S0140-6736(23)02044-5

[2] Zhang Y, Shen T, Wang S, 2022, Progression from Prediabetes to Type 2 Diabetes Mellitus Induced by Overnutrition. Hormones (Athens), 21(4): 591–597. https://doi.org/10.1007/s42000-022-00399-2

[3] Centers for Disease Control and Prevention (CDC), 2013, Awareness of Prediabetes–United States, 2005–2010. MMWR Morb Mortal Wkly Rep, 62(11): 209–212.

[4] DeFronzo RA, Tobin JD, Andres R, 1979, Glucose Clamp Technique: A Method for Quantifying Insulin Secretion and Resistance. Am J Physiol, 237(3): E214–E223. https://doi.org/10.1152/ajpendo.1979.237.3.E214

[5] DeFronzo RA, Simonson D, Ferrannini E, 1982, Hepatic and Peripheral Insulin Resistance: A Common Feature of Type 2 (Non-Insulin-Dependent) and Type 1 (Insulin-Dependent) Diabetes Mellitus. Diabetologia, 23(4): 313–319. https://doi.org/10.1007/BF00253736

[6] Faerch K, Borch-Johnsen K, Holst JJ, et al., 2009, Pathophysiology and Aetiology of Impaired Fasting Glycaemia and Impaired Glucose Tolerance: Does It Matter for Prevention and Treatment of Type 2 Diabetes? Diabetologia, 52(9): 1714–1723. https://doi.org/10.1007/s00125-009-1443-3

[7] Magkos F, Mittendorfer B, 2009, Stable Isotope-Labeled Tracers for the Investigation of Fatty Acid and Triglyceride Metabolism in Humans In Vivo. Clin Lipidol, 4(2): 215–230. https://doi.org/10.2217/clp.09.9

[8] Li C, Ford ES, McGuire LC, et al., 2006, Trends in Hyperinsulinemia Among Nondiabetic Adults in the U.S. Diabetes Care, 29(11): 2396–2402. https://doi.org/10.2337/dc06-0289

[9] Rijkelijkhuizen JM, McQuarrie K, Girman CJ, et al., 2010, Effects of Meal Size and Composition on Incretin, Alpha-Cell, and Beta-Cell Responses. Metabolism, 59(4): 502–511. https://doi.org/10.1016/j.metabol.2009.07.039

[10] Kolb H, Kempf K, Röhling M, et al., 2020, Insulin: Too Much of a Good Thing is Bad. BMC Med, 18(1): 224. https://doi.org/10.1186/s12916-020-01688-6

[11] Ten S, Maclaren N, 2004, Insulin Resistance Syndrome in Children. J Clin Endocrinol Metab, 89(6): 2526–2539. https://doi.org/10.1210/jc.2004-0276

[12] Bonnet-Serrano F, Devin-Genteuil C, Thomeret L, et al., 2023, C-Peptide Level Concomitant with Hypoglycemia Gives Better Performances than Insulin for the Diagnosis of Endogenous Hyperinsulinism: A Single-Center Study of 159 Fasting Trials. Eur J Endocrinol, 188(2): lvad012. https://doi.org/10.1093/ejendo/lvad012

[13] Gastaldelli A, 2022, Measuring and Estimating Insulin Resistance in Clinical and Research Settings. Obesity (Silver Spring), 30(8): 1549–1563. https://doi.org/10.1002/oby.23503

[14] Gastaldelli A, Baldi S, Pettiti M, et al., 2000, Influence of Obesity and Type 2 Diabetes on Gluconeogenesis and Glucose Output in Humans: A Quantitative Study. Diabetes, 49(8): 1367–1373. https://doi.org/10.2337/diabetes.49.8.1367

[15] Ferrannini E, Groop LC, 1989, Hepatic Glucose Production in Insulin-Resistant States. Diabetes Metab Rev, 5(8): 711–726. https://doi.org/10.1002/dmr.5610050806

[16] Bergman M, Abdul-Ghani M, DeFronzo RA, et al., 2020, Review of Methods for Detecting Glycemic Disorders. Diabetes Res Clin Pract, 165: 108233. https://doi.org/10.1016/j.diabres.2020.108233. Erratum in Diabetes Res Clin Pract, 180: 108632. https://doi.org/10.1016/j.diabres.2020.108632

[17] Gastaldelli A, Harrison SA, Belfort-Aguilar R, et al., 2009, Importance of Changes in Adipose Tissue Insulin

Resistance to Histological Response During Thiazolidinedione Treatment of Patients with Nonalcoholic Steatohepatitis. Hepatology, 50(4): 1087–1093. https://doi.org/10.1002/hep.23116

[18] Søndergaard E, Espinosa De Ycaza AE, Morgan-Bathke M, et al., 2017, How to Measure Adipose Tissue Insulin Sensitivity. J Clin Endocrinol Metab, 102(4): 1193–1199. https://doi.org/10.1210/jc.2017-00047

[19] Ter Horst KW, van Galen KA, Gilijamse PW, et al., 2017, Methods for Quantifying Adipose Tissue Insulin Resistance in Overweight/Obese Humans. Int J Obes (Lond), 41(8): 1288–1294. https://doi.org/10.1038/ijo.2017.110

[20] Ferrannini E, Bjorkman O, Reichard GA Jr, et al., 1985, The Disposal of an Oral Glucose Load in Healthy Subjects. A Quantitative Study. Diabetes, 34(6): 580–588. https://doi.org/10.2337/diab.34.6.580

[21] Abdul-Ghani MA, Matsuda M, Balas B, et al., 2007, Muscle and Liver Insulin Resistance Indexes Derived from the Oral Glucose Tolerance Test. Diabetes Care, 30(1): 89–94. https://doi.org/10.2337/dc06-1519

[22] Van der Kolk BW, Vogelzangs N, Jocken JWE, et al., 2019, Plasma Lipid Profiling of Tissue-Specific Insulin Resistance in Human Obesity. Int J Obes (Lond), 43(5): 989–998. https://doi.org/10.1038/s41366-018-0189-8

[23] Van der Kolk BW, Kalafati M, Adriaens M, et al., 2019, Subcutaneous Adipose Tissue and Systemic Inflammation Are Associated With Peripheral but Not Hepatic Insulin Resistance in Humans. Diabetes, 68(12): 2247–2258. https://doi.org/10.2337/db19-0560

[24] Song Y, Manson JE, Tinker L, et al., 2007, Insulin Sensitivity and Insulin Secretion Determined by Homeostasis Model Assessment and Risk of Diabetes in a Multiethnic Cohort of Women: The Women's Health Initiative Observational Study. Diabetes Care, 30(7): 1747–1752. https://doi.org/10.2337/dc07-0358

[25] Matsuda M, DeFronzo RA, 1999, Insulin Sensitivity Indices Obtained from Oral Glucose Tolerance Testing: Comparison with the Euglycemic Insulin Clamp. Diabetes Care, 22(9): 1462–1470. https://doi.org/10.2337/diacare.22.9.1462

[26] Reaven GM, Hollenbeck CB, Chen YD, 1989, Relationship Between Glucose Tolerance, Insulin Secretion, and Insulin Action in Non-Obese Individuals with Varying Degrees of Glucose Tolerance. Diabetologia, 32(1): 52–55. https://doi.org/10.1007/BF00265404

[27] Ahrens B, Taborsky G Jr., 2002, B-Cell Function and Insulin Secretion, in Baron A, Porte D, Sherwin RS (eds), Ellenberg and Rifkin's Diabetes Mellitus. McGraw-Hill Professional, New York, 43–65.

[28] Defronzo RA, 2009, Banting Lecture. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. Diabetes, 58(4): 773–795. https://doi.org/10.2337/db09-9028

[29] Wallace TM, Levy JC, Matthews DR, 2004, Use and Abuse of HOMA Modeling. Diabetes Care, 27(6): 1487–1495. https://doi.org/10.2337/diacare.27.6.1487

[30] Stefan N, Fritsche A, Schick F, et al., 2016, Phenotypes of Prediabetes and Stratification of Cardiometabolic Risk. Lancet Diabetes Endocrinol, 4(9): 789–798. https://doi.org/10.1016/S2213-8587(16)00082-6

[31] Oosterman JE, Wopereis S, Kalsbeek A, 2020, The Circadian Clock, Shift Work, and Tissue-Specific Insulin Resistance. Endocrinology, 161(12): bqaa180. https://doi.org/10.1210/endocr/bqaa180

[32] Hall KD, Chen KY, Guo J, et al., 2016, Energy Expenditure and Body Composition Changes After an Isocaloric Ketogenic Diet in Overweight and Obese Men. Am J Clin Nutr, 104(2): 324–333. https://doi.org/10.3945/ajcn.116.133561

[33] Ludwig DS, Ebbeling CB, 2018, The Carbohydrate-Insulin Model of Obesity: Beyond "Calories In, Calories Out". JAMA Intern Med, 178(8): 1098–1103. https://doi.org/10.1001/jamainternmed.2018.2933

[34] Barnosky AR, Hoddy KK, Unterman TG, et al., 2014, Intermittent Fasting vs Daily Calorie Restriction for Type 2 Diabetes Prevention: A Review of Human Findings. Transl Res, 164(4): 302–311. https://doi.org/10.1016/

j.trsl.2014.05.013

[35] Trussardi Fayh AP, Lopes AL, Fernandes PR, et al., 2013, Impact of Weight Loss With or Without Exercise on Abdominal Fat and Insulin Resistance in Obese Individuals: A Randomised Clinical Trial. Br J Nutr, 110(3): 486–492. https://doi.org/10.1017/S0007114512005442

[36] Tremblay A, Pelletier C, Doucet E, et al., 2004, Thermogenesis and Weight Loss in Obese Individuals: A Primary Association with Organochlorine Pollution. Int J Obes Relat Metab Disord, 28(7): 936–939. https://doi.org/10.1038/sj.ijo.0802527

[37] Melanson KJ, Summers A, Nguyen V, et al., 2012, Body Composition, Dietary Composition, and Components of Metabolic Syndrome in Overweight and Obese Adults After a 12-Week Trial on Dietary Treatments Focused on Portion Control, Energy Density, or Glycemic Index. Nutr J, 11: 57. https://doi.org/10.1186/1475-2891-11-57