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Original Article

Lipoprotein insulin resistance score and risk of incident diabetes during extended follow-up of 20 years: The Women's Health Study

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BACKGROUND: Type II diabetes (T2D) is preceded by prolonged insulin resistance and relative insulin deficiency incompletely captured by glucose metabolism parameters, high-density lipoprotein (HDL) cholesterol and triglycerides.

OBJECTIVE: Whether lipoprotein insulin resistance (LPIR) score, a metabolomic marker, is associated with incident diabetes and improve risk reclassification over traditional markers on extended follow-up.

METHODS: Among 25,925 nondiabetic women aged 45 years or older, LPIR was measured by nuclear magnetic resonance spectroscopy as a weighted score of very low density lipoprotein, low-density lipoprotein, and HDL particle sizes, and their subsets concentrations. We run adjusted cox regression models for LPIR with incident T2D (20.4 years median follow-up).

RESULTS: Adjusting for demographics, body mass index, life style factors, blood pressure, and T2D family history, the LPIR hazard ratio for T2D (hazard ratio [HR] per standard deviation, 95% confidence interval) was 1.95 (1.85, 2.06). Further adjusting for HbA1c, C-reactive protein, triglycerides, HDL and low-density lipoprotein cholesterol, LPIR HR was attenuated to 1.41 (1.31, 1.53) and had the strongest association with T2D after HbA1C in mutually adjusted models. The association persisted even in those with optimal clinical profiles, adjusted HR per standard deviation 1.91 (1.17, 3.13). In participants

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deemed at intermediate T2D risk by the Framingham Offspring T2D score, LPIR led to a net reclassification of 0.145 (0.117, 0.175).

CONCLUSION: In middle-aged or older healthy women followed prospectively over 20 years, LPIR was robustly associated with incident T2D, including among those with an optimal clinical metabolic profile. LPIR improved T2D risk classification and may guide early and targeted prevention strategies.

Introduction

Type II diabetes (T2D) is a global epidemic with increasing prevalence worldwide.[1] Since T2D is preceded by prolonged preclinical insulin resistance and beta cell dysfunction,[2,3] biomarkers of these early processes could identify and guide timely interventions in individuals susceptible to T2D. Despite glucose metabolism measures being good risk predictors and the benchmark for T2D diagnosis, current dysglycemia parameters are insensitive to incipient insulin resistance.[4] Nondiabetic individuals have alterations in hepatic lipoprotein metabolism due to insulin resistance that take place when glucose levels are still normal.[5] As insulin resistance is associated with future T2D, myocardial infarction, and overall mortality in nondiabetic subjects,[6–8] even earlier identification of such a process is of utmost importance.

Conventional lipoprotein metabolism biomarkers, such as high-density lipoprotein cholesterol (HDL-C) and triglycerides correlate with insulin resistance and incident T2D.[9,10] However, they do not reflect detailed insulin-resistant dyslipoproteinemia. This is characterized by hypersecretion of triglyceride-rich very low-density lipoprotein particles (VLDL-P) followed by concerted actions of lipases and transferases, which leads to accumulation of small dense low-density lipoprotein particles (LDL-P) and reduction in large HDL particles.[11] Despite that each of these lipoproteins has been associated with insulin resistance and incident T2D,[12–16] single lipid or lipoprotein parameters may not reflect insulin-resistant dyslipoproteinemia overall.

Lipoprotein insulin resistance (LPIR) score is a novel composite metabolomic biomarker that captures the multidimensional effects of insulin resistance on the lipoprotein metabolic chain.[17] LPIR is a clinically available test measured by a targeted metabolomics approach using high throughput nuclear magnetic resonance spectroscopy. It is a weighted score of VLDL, LDL, and HDL particle sizes, and large VLDL, small LDL, and large HDL particle concentrations that are more strongly related to insulin resistance than each of its individual subclasses.[17] Recently, LPIR was associated with incident T2D in a prospective study,[12] even among individuals treated with high-intensity statin.[18] We hypothesized that LPIR may identify T2D risk years before dysglycemia onset and other metabolic derangements.

We addressed the association of baseline LPIR with incident T2D in a cohort of nondiabetic healthy middle-aged women at baseline (N = 25,925) followed prospectively for more than 20 years. We also examined if LPIR can enhance risk prediction over a composite clinical score for incident T2D.

Material and methods

Population study

We studied the Women's Health Study (WHS), a completed double blinded, placebo-controlled trial of low-dose aspirin and vitamin E on the prevention of primary cardiovascular events and cancer in apparently healthy female healthcare professionals aged ≥45 years.[19] Individuals were enrolled between 1992 and 1995 and followed prospectively through 2015. All participants signed written informed consent, approved by the Institutional Review Board of Brigham and Women's Hospital (Boston, MA). At enrollment, participants answered questionnaires for demographics, anthropometrics, medical history, and lifestyle behaviors. From 39,876 individuals, 28,345 consented to have a blood sample stored in liquid nitrogen. We excluded participants with baseline T2D diagnosis, glycated hemoglobin (HbA1c) ≥6.5%, those using lipid-lowering therapy, and those with no LPIR measurement, resulting in 25,925 individuals (Fig. 1).

Population characteristics

At study entry age, race, smoking, alcohol intake, physical activity, menopausal status, postmenopausal hormone use, and family history of diabetes were self-reported on questionnaires.[13] Body mass index (BMI) was measured by weight (kilograms) divided by height (meters) squared.

Laboratory parameters

Baseline blood was collected in ethylenediaminetetraacetic acid tubes and stored in liquid nitrogen (−170°C)