

Association Between Fasting Insulin and High-Sensitivity C-Reactive Protein Among Adults: NHANES 2005-2010

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INTRODUCTION: Type 2 diabetes affects over 28 million U.S. adults and an additional 84 million U.S. adults are estimated to have prediabetes¹. Current prevention and treatment efforts are not adequately addressing the issue as the prevalence of diabetes continues to rise^{1,2} and many continue to experience long-term complications¹. A growing body of literature demonstrates that inflammation is involved in the development, progression and long-term complications of type 2 diabetes (T2DM), and visceral adipose tissue and pro-inflammatory cytokines play a key role³⁻⁵. Hyperinsulinemia is also associated with numerous ill health effects⁶⁻⁹, including inflammation^{10,11}. What is less clear is the role of insulin in this inflammatory cascade. Understanding the relationship between insulin and inflammation may have important implications for the treatment and prevention of T2DM.

OBJECTIVE: The purpose of the present study is to examine the independent association between insulin and high-sensitivity c-reactive protein (hs-CRP), a key marker of systemic inflammation¹².

METHODS: The National Health and Nutrition Examination Survey (NHANES) is conducted by the National Centers for Disease Control. It includes a series of two-year cross-sectional observational surveys designed to assess health and nutrition status among non-institutionalized residents in the United States. NHANES 2005-2010 collects data on hs-CRP, fasting insulin level, obesity-related measurements and other characteristics, and provides a unique opportunity to examine the independent association between fasting insulin level and hs-CRP. Details of the sampling design and methodology are described in detail elsewhere¹³.

To examine the independent effects of insulin on hs-CRP, we included individuals who did not self-report a diagnosis of diabetes or the use of glucose-lowering medications. Prior studies found an association between fasting insulin and hs-CRP in a non-diabetic population^{10,11,14}, although how much this association is mediated by visceral adipose tissue remains unclear. Because insulin levels vary with T2DM duration and treatment, it is difficult to discern the relationship between insulin and hs-CRP in a population with type 2 diabetes. In this way, we reduced confounding due to hyperglycemia, beta cell failure and glucose-lowering medications. Furthermore, many studies examine the relationship between insulin and inflammation in populations with T2DM and hyperglycemia¹⁵, which makes it difficult to discern if observed effects are due to achieving glycemic control or a neutral or positive effect of insulin. Therefore, more research is needed to identify the independent effects of insulin on hs-CRP. Understanding such an association may have important implications for T2DM treatment. Exclusion criteria were (1) current pregnancy; (2) use of cholesterol-lowering medications; and (3) age less than 20 years. Generalized linear models with Gamma distribution and identity link function were conducted to estimate the associations due to the skewed distribution of hs-CRP.

RESULTS: The final sample included 4,884 participants with an average age of 46 ± 17 years. Of this sample, 49.9% were male and 50.1% were female. The racial distribution was as follows: 27.0% Hispanic, 49.1% non-Hispanic White, 18.9% Non-Hispanic Black and 5.0% other race or multi-racial. After

adjusting for age, race, gender, smoking status, physical activity, and poverty-income ratio, fasting insulin level was significantly associated with hs-CRP ($\beta=.0067$, $p=.01$), independent of waist circumference. Moreover, the associations between fasting insulin and hs-CRP were reduced by 65.8% when including visceral adipose tissue (operationalized as waist circumference) in the model compared to the case without it, indicating some role of visceral adipose tissue in modulating the relationship of insulin and hs-CRP.

DISCUSSION: This secondary analysis investigated the association between fasting insulin and hs-CRP. This study found a significant association between insulin and hs-CRP while controlling for age, race, gender, smoking status, physical activity, poverty-income ratio and waist circumference. This study confirms results of previous research documenting the association between insulin and CRP while controlling for waist circumference¹⁴, suggesting this relationship is not entirely mediated by abdominal obesity. Therefore, this study extends our understanding of the relationship between insulin and hs-CRP.

The independent association between insulin and hs-CRP has implications for treatment options recommended to those with type 2 diabetes. Current T2DM treatment guidelines recommend specific glycemic targets without consideration for the treatments' effect on insulin¹⁶. However, if higher insulin levels are associated with higher levels of inflammation, it would be prudent to use therapies that reduce both insulin and glucose levels such as a carbohydrate-restricted diet. Insulin levels are frequently increased through medication to achieve glycemic control in individuals with type 2 diabetes¹⁷. If insulin causes increased inflammation, treatment approaches that simultaneously decrease insulin levels as well as glucose, may improve long-term outcomes for patients. Although treatment goals for type 2 diabetes do not currently address inflammation¹⁶, research suggests that decreasing inflammation may improve long-term outcomes⁴. Therefore, future studies are needed to evaluate the effect of therapeutic approaches that simultaneously decrease insulin and glucose levels, on long-term complications for type 2 diabetes.

Limitations exist in the present study due to the nature of cross sectional studies and the inability to determine causal effects. The interplay between insulin and inflammation is complex and likely different based on the level of metabolic dysfunction present. Despite this limitation, this study does provide insight into the independent association between insulin and hs-CRP in adults without diabetes. Additional research is needed to increase our understanding of this relationship.

CONCLUSION: This study found an association between insulin and hs-CRP while controlling for waist circumference, demonstrating a relationship separate from the effects of abdominal obesity. These results suggest that treatment approaches that simultaneously decrease insulin levels while decreasing glucose levels may provide additional anti-inflammatory effects, and therefore may improve long-term outcomes for those diagnosed with type 2 diabetes.

Title:

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Abstract Summary:

Treatment recommendations for type 2 diabetes focus on glycemic goals. Inflammation may be an additional target to improve outcomes, and insulin may play a role in the inflammatory process. The purpose of this study was to examine the association between insulin and high-sensitivity C-reactive protein (hs-CRP).

Content Outline:

Introduction: Prevalence of diabetes and current gaps in treatment

Review: Type 2 diabetes, hyperinsulinemia and inflammation

Methods: Secondary analysis of NHANES

Results: Association between fasting insulin and hs-CRP

Discussion: Implications for treatment recommendations

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Professional Experience: Ms. Missel began her career as a registered nurse in 2005, and she obtained her Master of Science in Community Health Nursing in 2010. She has worked as a diabetes educator and nurse clinician since 2015. In 2017 she returned to school to earn her PhD. Ms. Missel is currently funded as a Robert Wood Johnson Foundation Future of Nursing Scholar. Over the past year she has also gained research experience working as a research assistant for her mentor Laura Saslow as well as through a laboratory group consisting of researchers and students. The focus is in research related to type 2 diabetes and prediabetes prevention and treatment, with an emphasis on diet and lifestyle interventions.

Author Summary: Amanda Missel, MS, RN, a Robert Wood Johnson Foundation Future of Nursing Scholar, is interested in diabetes prevention and treatment. She is currently focusing her research on dietary interventions to decrease insulin levels and inflammation. She earned her BSN and MS in Community Health Nursing from the University of Michigan. She currently works as a Nurse Clinician at the Sparrow Diabetes, Endocrinology and Metabolics.

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Professional Experience: 2010- Ongoing collaboration (Well-being, Technologically-Enhanced Interventions), UCSF 2012- Ongoing collaboration (Diet Interventions), UCSF 2015- Assistant Professor, U Michigan, School of Nursing 2016, 2017 Sole Instructor for Introduction to the Research Approach in Nursing, UM Dr. Saslow is currently working on optimizing her online, very low-carbohydrate diet program for adults with type 2 diabetes, and is also studying the impacts of a very low-carbohydrate diet for adults with prediabetes or type 2 diabetes using in-person programs. She is also leading a study to compare the impact of a very low-carbohydrate diet vs. a Dietary Approaches to Stop Hypertension (DASH) diet on hypertension, glucose control, and weight in overweight adults with hypertension and prediabetes or type 2 diabetes.

Author Summary: Dr. Saslow's research is focused on creating and optimizing multicomponent, psychologically enhanced interventions that support long-term dietary adherence for the treatment and prevention of chronic diseases.

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Professional Experience: 6/2011-6/2015 Resident in Internal Medicine-Pediatrics, University of Michigan, Ann Arbor, MI 7/2015-6/2017 Robert Wood Johnson Foundation Clinical Scholars Program (VA Scholar), Ann Arbor, MI 7/2017-6/2018 VA Research Fellow with the University of Michigan 7/1/2018-present Clinical Lecturer, Department of Internal Medicine, University of Michigan, Ann Arbor, MI Dr. Griauzde completed the Robert Wood Johnson Foundation Clinical Scholars program and a Master of Science at the University of Michigan. She then completed an additional year of health services research training through the Veterans Health Administration. During this training, she acquired foundational experience with secondary data analysis, qualitative research methods, and behavioral health intervention design and evaluation. Dr. Griauzde served as the principle investigator on two pilot studies: 1) a 3-arm pilot randomized controlled trial to test a mobile health program among individuals with prediabetes and 2) a single-arm pilot study to test a low-carbohydrate Diabetes Prevention Program among individuals with prediabetes.

Author Summary: Dr. Griauzde is a health services researcher and primary care physician in the Department of Internal Medicine at the University of Michigan. She is particularly interested in creating and optimizing personalized, yet highly scalable, approaches to type 2 diabetes prevention.

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Professional Experience: Dr. Richardson was the Director of the Veterans Administration Diabetes Quality Improvement Initiative (QUERI) and conducted a multi-site implementation study of the Diabetes Prevention Program for veterans. Dr. Richardson currently serves as Associate Chair for Research Programs in the Department of Family Medicine. She currently serves as a member of the Institute for Health Policy and Innovation's Institute Leadership Team (ILT). In addition, she leads education and scholarship initiatives as Chair of the IHPI education committee and co-director of the IHPI Clinician Scholars Program (NCSP). Dr. Richardson also serves as Associate Editor of the American Journal of Preventive Medicine.

Author Summary: Dr. Richardson is a physical activity and diabetes prevention researcher who emphasizes the importance of using low-cost and scalable approaches to promoting physical activity. She develops and tests behavioral internet-mediated interventions to increase physical activity, decrease weight, and prevent diabetes.

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Professional Experience: Dr. Liu obtained his master and doctoral degrees in statistics from the University of Florida. There are two lines in his research: development of novel statistical models and application of standard statistical techniques in health sciences. In statistical methods, his interests include, but not limited to, computationally extensive statistics (MCMC algorithms, modified EM algorithms

and GEE), Big Data analysis, Bayesian statistics, joint longitudinal, survival and stochastic models with non-ignorable missing mechanism, multi-level models, latent variable models and covariance models. In health sciences, Dr. Liu has a broad interest in hypertension, cardiovascular and renal diseases, racial disparity, and genetic variants for mental disorder and substance use.

Author Summary: Dr. Liu's research areas include analytic models and techniques for cardiovascular and renal outcomes (congestive heart failure, heart attack, hypertension, diabetes, stroke), high dimensional methods for genome wide association study of mental disorders (Alzheimer's disease, bipolar disorder, epilepsy, schizophrenia, neuroticism, attention-deficit hyperactivity disorder) and substance dependence (alcohol, nicotine, drug), and epidemiologic methods for cancer (lung cancer, colorectal cancer, prostate cancer).