HHS Public Access

Author manuscript

Diabet Med. Author manuscript; available in PMC 2018 February 01.

Published in final edited form as:

Diabet Med. 2017 February ; 34(2): 235–238. doi:10.1111/dme.13139.

Brain natriuretic peptide and insulin resistance in older adults

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Abstract

Aims—Higher levels of brain natriuretic peptide (BNP) have been associated with a decreased risk of diabetes in adults, but whether BNP is related to insulin resistance in older adults has not been established.

Methods—N-Terminal (NT)-proBNP was measured among Cardiovascular Health Study participants at the 1989–1990, 1992–1993 and 1996–1997 examinations. We calculated measures of insulin resistance [homeostatic model assessment of insulin resistance (HOMA-IR), quantitative insulin sensitivity check index (QUICKI), Gutt index, Matsuda index] from fasting and 2-h concentrations of glucose and insulin among 3318 individuals with at least one measure of NT-proBNP and free of heart failure, coronary heart disease and chronic kidney disease, and not

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Competing interests

None disclosed.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Histogram of allelic score in men and women.

taking diabetes medication. We used generalized estimating equations to assess the cross-sectional association of NT-proBNP with measures of insulin resistance. Instrumental variable analysis with an allele score derived from nine genetic variants (single nucleotide polymorphisms) within or near the *NPPA* and *NPPB* loci was used to estimate an un-confounded association of NT-proBNP levels on insulin resistance.

Results—Lower NT-proBNP levels were associated with higher insulin resistance even after adjustment for BMI, waist circumference and other risk factors ($P < 0.001$ for all four indices). Although the genetic score was strongly related to measured NT-proBNP levels amongst European Americans (F statistic = 71.08), we observed no association of genetically determined NT-proBNP with insulin resistance ($P = 0.38$; $P = 0.01$ for comparison with the association of measured levels of NT-proBNP).

Conclusions—In older adults, lower NT-proBNP is associated with higher insulin resistance, even after adjustment for traditional risk factors. Because related genetic variants were not associated with insulin resistance, the causal nature of this association will require future study.

Introduction

B-Type or brain natriuretic peptide (BNP) is released by the heart in response to haemodynamic stress and results in vasodilation and diuresis. Natriuretic peptides may also influence metabolic disease [1]. Prospective studies have demonstrated an inverse association between BNP and risk for Type 2 diabetes [2], and a pooled analysis of the rs198389 variant in *NPPB* suggested that higher genetically determined BNP levels may reduce diabetes risk [3,4] although an instrumental variable analysis to estimate the effect of genetically determined NT-proBNP levels on diabetes was null.

Here, we sought to determine whether endogenous NT-proBNP levels are associated with decreased insulin resistance, as measured by indices derived from fasting steady-state and dynamic tests of glucose and insulin in the Cardiovascular Health Study (CHS). We also conducted an instrumental variable analysis using a single nucleotide polymorphism (SNP) score derived from nine genetic variants (SNPs) in European Americans within or near the *NPPA* and *NPPB* loci to estimate the genetically determined effect of NT-proBNP on insulin resistance.

Subjects and Methods

The Cardiovascular Health Study is a population-based prospective study of older men and women age 65 or older at four U.S. field centres. Institutional boards at each of the field centres and the University of Washington approved this study. Individuals provided written informed consent; only those who consented specifically to the use of genetic data were included in the genetic analyses.

NT-proBNP was measured in frozen specimens collected from participants in the Cardiovascular Health Study in 1989–1990, 1992–1993 and 1996–1997. Measurements of NT-proBNP were performed using commercially available immunoassays (Roche Diagnostic Elescys proBNP Assay, Indianapolis, IN, USA).

Assessment of insulin resistance

Glucose and insulin were measured after an overnight fast of at least 8 h at the 1989–1990, 1992–1993 and 1996–1997 examinations, and again 2 h after a 75 g oral glucose challenge (OGTT) at the examinations in 1989–1990 and 1996–1997. We used four indices of insulin resistance and/or sensitivity utilizing either static fasting values or values obtained from dynamic testing: homeostasis model assessment for insulin resistance (HOMA-IR) [5], the Gutt insulin sensitivity index [6], quantitative insulin sensitivity check index (QUICKI) [7] and the Matsuda sensitivity index [8].

Covariates

Smoking status and alcohol consumption were based on self-report. Leisure time physical activity (kcal/week) was assessed using a modified Minnesota Leisure Time Activities questionnaire [9]. Information on prescription medications taken in the previous 2 weeks was collected by medication inventory [10]. Body weight, height, waist circumference and blood pressures (BP) were measured using standardized protocols. Missing covariate values were carried forward from previous examinations, if available. We included serum C-reactive protein, lipids and adiponectin as pre-specified covariates.

Genotyping

We used genetic variants genotyped in the Cardiovascular Health Study as part of the CARe consortium, an NHLBI-led collaboration of several cohort studies [11,12]. In total, nine SNPs were genotyped among populations of European descent (rs17350396, rs14078, rs198358, rs5068, rs17376426, rs198372, rs11802855, rs6694164 and rs198388; Fig. S1) and 10 among African Americans (rs17350396, rs14078, rs198358, rs5068, rs17376426, rs198372, rs11802855, rs6694164, rs198388 and rs5064).

Statistical analysis

We excluded individuals who had heart failure, coronary heart disease, chronic kidney disease (cystatin-based estimated glomerular filtration rate < 60 ml/min/1.73 m^2), or treated diabetes at or prior to each NT-proBNP measurement. A total of 6274 NT-proBNP measurements among 3318 individuals were available for analysis (1171 people contributed one measurement, 1338 contributed two and 809 contributed three). Participants were categorized by NT-proBNP concentrations, based on quartiles of the distribution of all available measurements. To assess the cross-sectional association of NT-proBNP and measures of insulin resistance, we used generalized estimating equation regression models with robust standard errors to account for correlation among repeated measures. Model 1 was adjusted for age, sex, race (black, non-black) and recruitment wave. Model 2 was further adjusted for BMI, waist circumference, systolic BP, diastolic BP, LDL-cholesterol, HDL-cholesterol, triglycerides, C-reactive protein, cystatin-based estimated glomerular filtration rate, anti-hypertensive medication, smoking status (never, former, current), alcohol consumption (none, < 7 drinks/week, ≥ 7 drinks/week) and self-reported health status (excellent, very good, good, fair, poor). We evaluated the potential confounding effect of adiponectin by fitting a model that included Model 2 covariates in people who had measured levels of adiponectin (n = 3880).

We performed an instrumental variable analysis to estimate the effect of genetically determined NT-proBNP levels on insulin sensitivity. We first created an allele score separately in European Americans and African Americans by summing the number of NT-proBNP-increasing alleles in each SNP. We then used a two-stage least squares approach to estimate the difference in HOMA-IR per doubling in genetically predicted NT-proBNP. In the first step, genetically determined NT-proBNP levels were estimated as a function of the allele score. In the second step, the predicted values of NT-proBNP from the first model were used as independent variables in a second model with HOMA-IR as the outcome. We compared the differences in insulin resistance from analyses using measured NT-proBNP concentrations and instrumentally predicted NT-proBNP using the Wooldridge test. To reduce weak instrument bias, we only present results where the first-stage *F* statistic exceeded 12.

Results

NT-proBNP levels ranged from 0.5 to 722.2 pg/ml with a 10-fold difference in median NT-proBNP levels between the lowest and highest quartile.

People in the highest quartile of NT-proBNP had significantly lower measures of insulin resistance (HOMA-IR) and higher insulin sensitivity (QUICKI, Matsuda index, Gutt index) than those in the lowest NT-proBNP quartile (Table 1). The results did not change appreciably after further adjustment for covariates and BMI, waist circumference, systolic and diastolic BP, and lipids. Results were also similar after excluding observations with NT-proBNP > 900 pg/ml or further adjusting for adiponectin.

Association of genetically determined NT-proBNP levels and HOMA-IR

A total of 4429 EA and 625 AA Cardiovascular Health Study participants had complete genetic and metabolic data. The nine-SNP allele score was very strongly related to measured NT-proBNP levels in European Americans [increase in NT-proBNP with each additional allele in the nine-SNP risk score 10.7%; 95% confidence interval (95% CI): 8.2% to 13.1%; *F* statistic 71.08], but not in the smaller population of African Americans in the Cardiovascular Health Study (*F* statistic 11.39).

We did not detect any significant association between genetically determined NT-proBNP and insulin resistance using an instrumental variable approach using the SNP score. A doubling of measured NT-proBNP levels was associated with a 0.28 decrease in HOMA-IR (95% CI −0.34, −0.21) in European Americans, but the corresponding estimate for a doubling of genetic NT-proBNP levels was a 0.18 increase in HOMA-IR (95% CI −0.21, 0.56). The genetic and observed effects differed significantly ($P = 0.01$), raising the possibility of residual confounding in measured NT-proBNP levels. Further adjustment for minor differences in SNP score according to sex and smoking did not alter these findings.

Discussion

In this study of older adults, lower NT-proBNP levels were associated with higher insulin resistance. The robustness of this finding is supported by multivariable analysis with a wide

range of clinical and laboratory covariates and the utilization of four complementary measures of insulin sensitivity that incorporated both fasting and post-load glucose and insulin values. However, using genetic variants as instruments to assess the potentially causal association between NT-proBNP and insulin resistance suggested that the measured and genetically predicted associations differed, although a modest inverse association of even genetic NT-proBNP levels with insulin resistance cannot be excluded.

These cross-sectional data cannot establish whether low NT-proBNP levels precede or follow the development of insulin resistance. Indeed, lower NT-proBNP could be a consequence rather than a cause of insulin resistance [13]. To address this possibility, we derived a genetic allele score from SNPs in or near the *NPPA* and *NPPB* loci. The score correlated strongly with measured NT-proBNP levels, but genetically estimated levels of NT-proBNP did not associate with insulin resistance.

Several possible reasons for the disparity in the association between plasma and genetically determined NT-proBNP and insulin resistance exist. One possibility is that observed observation between reduced NT-proBNP and insulin resistance is confounded by other determinants of NT-proBNP levels, whereas genotype is not. For example, early undiagnosed heart failure, which increases NT-proBNP levels, may increase metabolic demands and reduce adipose stores. Longitudinal studies with repeated measures of adiposity may inform this issue, as would assessments of glycaemic status in trials of nesiritide.

Our study is not without limitation. Our results are cross-sectional and we cannot exclude confounding or reverse causation. Although we evaluated a large number of people with repeated measures of multiple indices of insulin resistance, the precision of our genetic analyses, particularly in African Americans, was limited. Although our focus upon older adults, who have the highest prevalence of insulin resistance, was intentional, our results may not apply to younger adults, in whom genetic effects may be more pronounced.

In conclusion, higher NT-proBNP levels are associated with greater insulin sensitivity in older adults, but findings from genetic analyses do not clearly support a causal role. Additional studies to define the causal effect of BNP on insulin resistance may shed light on this intriguing association.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding sources

This research was supported by contracts HHSN268201200036C, HHSN268200800007C, N01HC55222, N01HC85079, N01HC85080, N01HC85081, N01HC85082, N01HC85083, N01HC85086, and grants U01HL080295 and R01HL094555 from the National Heart, Lung, and Blood Institute (NHLBI), with additional contribution from the National Institute of Neurological Disorders and Stroke (NINDS). Additional support was provided by R01AG023629 from the National Institute on Aging (NIA). A full list of principal Cardiovascular Health Study investigators and institutions can be found at CHS-NHLBI.org. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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What's new?

- In older adults, lower N-terminal pro-brain natriuretic peptide is associated with markedly higher insulin resistance even after adjustment for traditional risk factors, but a genetic score using related variants was not.

Table 1

Adjusted mean levels of insulin sensitivity measures by NT-proBNP category

		NT-proBNP (pg/ml)				
		≤ 60.0	> 60.0–109.9	> 109.9–199.9	> 199.9	
	Unadjusted mean (SD)	Adjusted difference (95% CI)				*P* trend
HOMA-IR						
Model 1 (*n* = 6274)	3.54 (2.23)	Ref.	−0.482 (−0.645, −0.320)	−0.723 (−0.896, −0.550)	−0.987 (−1.162, −0.811)	< 0.001
Model 2 (*n* = 6016)		Ref.	−0.423 (−0.572, −0.274)	−0.584 (−0.747, −0.421)	−0.837 (−1.00, −0.671)	< 0.001
QUICKI						
Model 1 (*n* = 6274)	0.32 (0.020)	Ref.	0.004 (0.003, 0.005)	0.007 (0.006, 0.008)	0.010 (0.008, 0.011)	< 0.001
Model 2 (*n* = 6016)		Ref.	0.003 (0.002, 0.005)	0.006 (0.005, 0.007)	0.009 (0.007, 0.010)	< 0.001
Matsuda Index						
Model 1 (*n* = 3498)	3.63 (2.26)	Ref.	0.225 (0.033, 0.417)	0.581 (0.374, 0.788)	0.861 (0.628, 1.09)	< 0.001
Model 2 (*n* = 3367)		Ref.	0.187 (0.004, 0.370)	0.509 (0.307, 0.710)	0.776 (0.584, 1.00)	< 0.001
Gutt Index						
Model 1 (*n* = 3494)	60.30 (24.93)	Ref.	2.84 (0.71, 4.96)	5.00 (2.74, 7.26)	7.31 (4.78, 9.83)	< 0.001
Model 2 (*n* = 3367)		Ref.	2.48 (0.44, 4.52)	4.27 (2.04, 6.49)	6.61 (4.11, 9.12)	< 0.001

N-terminal pro-natriuretic peptide