Published in final edited form as:

Metabolism. 2015 August ; 64(8): 857–861. doi:10.1016/j.metabol.2015.04.001.

The association between N-terminal pro B-type natriuretic peptide and lipoprotein particle concentration plateaus at higher N-terminal pro B-type natriuretic peptide values: Multi-Ethnic Study on Atherosclerosis

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Abstract

Background—The association between N-terminal pro B-type natriuretic peptide (NT-proBNP) and blood levels of small and large LDL- and HDL- particle (P) concentration may not be linear throughout the whole range of NT-proBNP values.

Methods—Linear spline regression analysis between NT-proBNP and lipoprotein particle concentrations was performed cross-sectionally in 5597 individuals from the Multi-Ethnic Study of Atherosclerosis adjusted for age, race, sex, body mass index, % of energy from saturated fats, intentional exercise, statin use, antihypertensive medication use, diabetes, IL-6 and estimated

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Authors' Contribution

OAS performed the statistical analysis and prepared the manuscript. AM, CAP and LBD provided critical discussion of the results and interpretation. JDO performed the analysis to measure lipoprotein particles and also provided comments on the methods used in this manuscript. DAD and HB provided important clinical comments for this manuscript. DRJ Jr. contributed with his expertise in statistical analysis.

Disclosures

Otto A. Sanchez, no disclosures. Carmen A. Peralta, no disclosures. Joao A. Lima, consultant to Toshiba Medical Systems, Bracco. Hossein Bahrami, no disclosures. David R Jacobs, no disclosures.

All authors have approved the final version of this manuscript.

glomerular filtration rate. Spline knots were selected as the point at which the linear slope changed in these associations.

Results—NT-proBNP was positively associated with large LDL-P and HDL-P, but inversely associated with small LDL-P and HDL-P, but only for NT-proBNP values below the knot (range: 100–200 pg/mL).

Conclusion—These results suggest the presence of two distinct biological mechanisms above and below the knot determining the association between NT-proBNP and lipoprotein particle concentrations.

Keywords

NT-proBNP; Lipoprotein particles; MESA study; Nuclear magnetic resonance spectroscopy

1. Introduction

B-type natriuretic peptide (BNP), which is associated with an increased risk of morbidity and mortality from cardiovascular disease [1], could potentially be involved in modifying lipoprotein particle concentration because of its effect on lipid oxidation and lipolysis [2,3]. This is important because prospective cohort studies and clinical trials have shown that low density lipoprotein particle (LDL-P) and small high density lipoprotein particle (HDL-P) concentrations are positively associated with an increased risk of cardiovascular disease (CVD) [4,5] and coronary heart disease (CHD) events [6].

The association between blood lipids concentrations and glucose with NT-proBNP does not follow a linear association throughout the whole range of NT-proBNP values [7]. For NT-proBNP levels <100 pg/mL, we suggested that variations in NT-proBNP occur in response to physiological events. However, within the range in which pathophysiology presumably plays a primary role in determining BNP levels (≥ 100 pg/mL) the influence of pathological factors (subclinical CVD and inflammation) becomes progressively more important leading to substantial elevations in NT-proBNP and blunting of the physiological effects of natriuretic peptides on lipid metabolism [7].

We hypothesized that NT-proBNP is inversely associated with small LDL-P and HDL-P, but positively associated with large LDL-P and HDL-P. We also hypothesized that this effect does not follow a linear association throughout the whole range of NT-proBNP, but that plateaus occur at presumably pathophysiological levels of NT-proBNP.

2. Methods

2.1. Study Subjects

Participants eligible for this study were 5597 of the 6814 from the Multi-Ethnic Study of Atherosclerosis (MESA) in whom NT-proBNP and concentrations of lipoprotein particles were measured at their baseline visit in 2000–2002. They were men and women ages 45–84 years, of white, black, Chinese, and Hispanic race/ethnicity, initially free of overt CVD. Details of study recruitment and design have been published [8]. The institutional review

boards at all participating centers approved the study and written informed consent was obtained from every participant prior to data collection.

2.2. Blood Measurements

Blood samples were drawn following a 12 h fast and processed according to published methods [9]. Plasma NT-proBNP was measured at the Veterans Affairs San Diego Health Care System, using an ElecSys 2010 analyzer (Roche Diagnostics, Indianapolis, IN) [10,11]. Interleukin-6 (IL-6) was measured as previously described [7]. Lipoprotein particle concentration was determined at LipoScience, Inc. (Raleigh, NC) by nuclear magnetic resonance spectroscopy using the LipoProfile-3 algorithm. The intra-assay coefficient of variation for LDL-P, HDL-P and VLDL-P was 4%, 0.9% and 6.3%, respectively [12]. Serum creatinine levels were used to estimate glomerular filtration rate (eGFR) according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula [13].

2.3. Covariates

Age, race/ethnicity, sex, body mass index (BMI) computed as weight (kg)/height² (meters), % of total energy intake from saturated fats, total intentional exercise (MET-min/week), statin use, antihypertensive medication use and presence of diabetes, IL-6 and eGFR were assessed using standard protocols, as previously reported [13–15]. Individuals were classified as having subclinical CVD if they had at least one of the following: left ventricular hypertrophy, intima media thickness > 1.3 mm, carotid plaque and coronary artery calcium score > 0 [16–19].

2.4. Statistical Analysis

Linear spline regression models with a single knot are described in detail in [7]. Linear spline regression models assessed the associations between baseline values of NT-proBNP as the predictor variable and the levels of small and large LDL-P, HDL-P, intermediate density lipoprotein-P (IDL-P) and very low density lipoprotein-P (VLDL-P) as dependent variables adjusting for the covariates listed above. The NT-proBNP values at which the slopes of the dependent variables had a substantial change in slope, i.e., the knot, were determined at NT-proBNP values every 5 pg/mL intervals between 20 and 300 pg/mL. The NT-proBNP value at which the linear spline model had the highest R² was chosen as the knot for each dependent variable. Significance was set at $p < 0.05$. Statistical analysis was performed using SAS v 9.3 by SAS Institute Inc., Cary, NC.

3. Results and Discussion

This sample has been described previously. In brief, about one third of the sample had NT-proBNP values > 100 pg/mL and were more likely to be females, have lower BMI, and have a greater proportion with subclinical CVD [7]. Table 1 shows the adjusted regression coefficients using linear splines and Fig. 1 (A–C) shows the plots of the adjusted lipoprotein particle concentration by deciles of NT-proBNP at MESA baseline. Regression coefficients of the slopes below the knot are on average 4 thousand times larger than the regression coefficients of the slopes above the knot. The knot varied between 30 and 200 pg/mL across lipoprotein particle variables. Large LDL-P and large and medium HDL-P had positive

associations below the knot and small LDL-P, small HDL-P and medium and small VLDL-P all had inverse associations with NT-proBNP below the knot. The association between NT-proBNP and lipoprotein particle concentrations plateaued above the knot in all cases, except for small VLDL-P. Further adjusting for plasma triglycerides slightly weakened the regression coefficients between NT-proBNP and the different lipoprotein particles, except for Small- and Large- VLDL-P, which became non-significant (data not shown). Adjusting for subclinical CVD did not substantially modify the regression coefficients (data not shown). These findings suggest that the association between NT-proBNP and lipoproteins particle concentration is largely independent of the presence of diabetes, inflammation plasma triglycerides and subclinical CVD.

A change in NT-proBNP from 40 to 100 pg/mL would be associated with a 20% lowering of small LDL-P showing that an elevation in NT-proBNP, within the physiological range, is associated with differences in lipoprotein particle concentration in a direction that would be assumed to lessen the risk of developing CVD [12].

We had previously described a biphasic association between NT-proBNP with blood lipids, glucose and BMI [7] and proposed that below the knot (the presumed physiological range) natriuretic peptides induce mitochondrial genesis, lipolysis and lipid oxidation [2,3,20]. On the other hand above the knot is the presumed pathophysiological range, which may result in response to subclinical or clinical conditions that cause cardiac strain and inflammation [21,22]. This could result in increased synthesis of biologically inactive natriuretic peptides, saturation of natriuretic peptide receptors, even in the absence of down-regulation or to a state of resistance to natriuretic peptides [23] and an association with an increased risk of morbidity and mortality from CVD [24].

Low levels of BNP can lead to mitochondrial dysfunction [2] and an increased synthesis of lipids, VLDL and ApoB-100 [25], the major apolipoprotein in VLDL and LDL [26]. The decreased oxidation of fat increases available free fatty acids that are then transferred to lipoproteins, producing triglyceride rich lipoproteins [27,28]. These physiological and biochemical pathways provide a biological explanation for the consequences of low BNP on blood lipids and it should be an additional factor to be considered in individuals with dyslipidemia and metabolic syndrome.

4. Strength and Limitations

The use of a well-validated technique with low intra-assay coefficient of variation to measure lipoprotein particle size concentrations [12] and the large multiethnic cohort free of cardiovascular disease in this cross-sectional study are factors that strongly support our results. Although choosing a cutoff value to differentiate the two phases of the association between NT-proBNP and lipoproteins is based on well-established statistical methods it should be carefully considered and we are not proposing that the values shown here should be taken as an absolute limit between physiological and pathological responses to the effects of natriuretic peptides. Therefore, dose-response experiments should be designed to study the relationship between natriuretic peptides and lipoprotein metabolism to determine the dose at which a linear association is strongly attenuated.

5. Conclusions

This study shows that the associations between NT-proBNP and lipoprotein particle concentrations do not follow a linear response throughout the whole range of NT-proBNP values, consistent with the idea that two distinct biological mechanisms are in play above vs below the knot.

Acknowledgments

The authors also thank the investigators staff and the participants of the Multi-Ethnic Study of Atherosclerosis (MESA) for their valuable contributions. A full list of MESA investigators and institutions can be found at <http://www.mesa-nhlbi.org/>.

Funding

This research was supported by contract N01-HC-95169 from the National Heart, Lung, and Blood Institute and by grants UL1-TR-000040 and UL1-TR-001079 from NCRR.

Daniel Duprez MD, PhD, consultant to Novartis Astra Zeneca. Lori B Daniels, consultant to Singlulex and Alere, Inc; speaking fees from Critical Diagnostics. Alan Maisel, consultant to Alere, BG Medicine, Brahms, Critical Diagnostics, EFG diagnostics, Novartis, Abbott. James D. Otvos, Chief Scientific Officer of Liposcience.

Abbreviations

BNP	B-type Natriuretic Peptide
CVD	Cardiovascular Disease
CHD	Coronary Heart Disease
NT-proBNP	Amino Terminal B-type Natriuretic Peptide
LDL-P	Low Density Lipoprotein Particle
HDL-P	High Density Lipoprotein Particle
IDL-P	Intermediate Density Lipoprotein Particle
VLDL-P	Very Low Density Lipoprotein Particle
MESA	Multi-Ethnic Study of Atherosclerosis
eGFR	Estimated Glomerular Filtration Rate
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration formula
BMI	Body Mass Index
MET	Metabolic Equivalents

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Fig. 1. Variations in lipoprotein particle concentration by deciles of NT-proBNP at MESA baseline. Data are presented as mean values $\pm$ SE for dependent variables at each decile of NT-proBNP adjusted for sex, race, age, BMI, % of total calories from saturated fats, total intentional exercise (MET-min/week), statin use, antihypertensive medication use and presence of diabetes, IL-6 and estimated glomerular filtration rate. (A) Small, large LDL-P

and Intermediate density lipoprotein (IDL-P), (B) small, medium and large HDL-P and (C) small, medium and large VLDL-P. P indicates lipoprotein particle.

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Table 1

Adjusted slopes for NT-proBNP estimating lipoprotein particle concentrations in linear spline models with a single knot. MESA baseline.

Dependent Variables	NT-proBNP knot (pg/mL)	R ²	Mean (SD) of NT-proBNP for values <knot (pg/mL)	b _{<knot}	p value for b _{<knot}	Mean (SD) of NT-proBNP for values >knot (pg/mL)	b _{>knot}	p value for b _{>knot}	p value for difference b _{>knot} minus b _{<knot}
Small LDL-P	100	0.18	39.9 (26.5)	-1.63	<0.0001	257.8 (426.6)	0.004	0.8	<0.0001
Large LDL-P	120	0.15	44.9 (31.3)	0.23	<0.0001	293.6 (468.4)	-0.0007	1.0	<0.0001
IDL-P	40	0.05	19.4 (11.1)	-0.57	<0.0001	155.6 (308.5)	-0.0008	0.9	<0.0001
Small HDL-P	200	0.10	59.5 (47.8)	-0.02	<0.0001	440.7 (638.3)	-0.0006	0.07	<0.0001
Medium HDL-P	145	0.10	50.3 (36.9)	0.02	<0.0001	339.0 (521.1)	-0.00005	0.9	<0.0001
Large HDL-P	115	0.18	43.8 (30.2)	0.005	<0.0001	285.0 (458.3)	-0.0002	0.2	<0.0001
Small VLDL-P	75	0.005	33.0 (20.7)	-0.009	0.02	216.6 (378.8)	0.003	0.01	0.0006
Medium VLDL-P	65	0.03	29.5 (18.1)	-0.09	<0.0001	198.6 (358.0)	0.0002	0.9	<0.0001
Large VLDL-P	30	0.07	14.9 (8.1)	-0.06	<0.0001	140.4 (291.1)	-0.0007	0.05	<0.0001

Abbreviations: HDL-P, LDL-P, IDL-P, VLDL-P represent high, low, intermediate, and very low density lipoprotein particles.

Adjusted for age, race/ethnicity, sex, body mass index (BMI), % of total energy intake from saturated fats, total intentional exercise (MET-min/week), statin use, antihypertensive medication use, presence of diabetes, IL-6 and estimated glomerular filtration rate. Each row represents a single linear spline model, that is, the regression equation is dependent variables = $a + b_{<knot} (NT-proBNP - knot) + b_{>knot} (NT-proBNP - knot) *$ where a = intercept and the knot was chosen as the NT-proBNP value between 20 and 300 pg/mL with the highest R². The adjusted b_{<knot} value is the slope for each dependent variable regressed on baseline NT-proBNP <knot, whereas b_{>knot} is the corresponding slope for baseline NT-proBNP >knot. Units of the regression coefficients b_{<knot} and b_{>knot} are nmol/L per pg/mL difference in NT-proBNP for LDL-P, IDL-P, and VLDL-P and umol/L per pg/mL difference in NT-proBNP for HDL-P.