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# The Way to a Man's Stomach Is Through His Heart?

## The Relation Between Natriuretic Peptide Levels and Adipose Tissue Distribution*

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The times are gone in which we all thought that the heart was just a mechanical pump and adipose tissue was where you stored your excess calories. Both the heart and adipose tissue have been recognized as part endocrine organ (1,2), while the interplay between these organs, and especially the effects of natriuretic peptides on adipose tissue, is receiving deserved attention (3).

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The natriuretic peptides atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and its nonactive peptide N-terminal pro–B-type natriuretic peptide (NT-proBNP) have all been studied extensively in relation to the treatment and diagnosis of hypertension and especially to heart failure in the case of BNP and NT-proBNP (4–7). Unexpectedly, in recent years, the effects of the natriuretic peptides have been found to extend beyond the vascular system.

ANP and BNP influence adipose tissue through binding to the natriuretic peptide receptors (NPRs). Binding of the natriuretic proteins to the NPR-A receptor leads to enhanced lipolysis (ANP > BNP) (8) and adiponectin secretion (9), whereas binding to the NPR-C or clearance receptor leads to degradation of the natriuretic proteins (4). Because observational studies found an inverse relation between plasma natriuretic peptide levels and body mass index (10), it was presumed that this relation could be explained by enhanced clearance of the natriuretic peptide via the NPR-C receptor in adipose tissue. A new problem arose when it was found that the nonactive peptide NT-proBNP, which is secreted simultaneously with BNP, had the same inverse relation with body mass index while not being cleared from the circulation by the NPR-C receptor.

In this issue of the *Journal*, Neeland et al. (11) show, using convincing methods, a relation between both higher plasma BNP and NT-proBNP levels and less visceral adipose tissue, liver fat, and increased lower body fat, independent of age, sex, race, and markers of adiposity. Some of the findings in the paper receive little or no attention: for example, the nonactive peptide NT-proBNP has a stronger inverse relation to visceral fat and liver fat than BNP. Because BNP is cleared from the circulation by the NPR-C receptors, which are especially abundant in the visceral adipose tissue compartment (12), should the stronger relation between NT-proBNP, and for example visceral fat, be seen as a proxy and more accurate representation of the relation between BNP and visceral fat which is just diluted by the clearance of BNP via the NPR-C receptor while still having its major beneficial effects through the NPR-A receptor? The study by Neeland et al., however, will not answer this question because it suffers from a problem that often occurs with observational etiologic studies: the precise causal relations remain unclear and, as always, further studies are needed.

One of the remaining questions is the precise role of adipose tissue. ANP reduces low-grade inflammation in adipose tissue (13), whereas the adipose tissue itself is instrumental in the regulation of plasma natriuretic peptide levels via the insulin-dependent expression of NPR-C (12). Not surprisingly, insulin resistance is associated with lower natriuretic peptide levels (14), which may also be an explanation for the relation Neeland et al. (11) found between natriuretic peptides and liver fat after adjustment for visceral fat. Because rapid reductions in adipose tissue, such as after bariatric surgery, are associated with an increase in the natriuretic peptides (15), and the expression of NPR-C on adipose tissue probably does not completely explain the relation between adipose tissue and plasma natriuretic peptide levels (16), we could speculate on the existence of a possible adipose tissue–derived feedback mechanism on the production of natriuretic peptides. Perhaps the way to a man's heart is through his stomach?

Finally, the least scientific but for some the most obvious question remains: the teleological one. To what purpose might

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we have such a connection between adipose tissue and the heart and vice versa? Although nature is not always obliged to give us these answers, we should ask the questions. Or to use a Dutch proverb: You have "No," you can get "Yes."

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**Key Words:** body fat distribution ■ insulin resistance ■ natriuretic peptides ■ visceral fat.