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REVIEW

The Role of Adiponectin and Brain Natriuretic Peptide in Predicting Cardiovascular Events

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List of Abbreviations:
ACE = angiotensin-converting enzyme
AMPK = adenosine monophosphate activated protein kinase
ANP = atrial natriuretic peptide
BNP = brain natriuretic peptide
CNP= C-type natriuretic peptide
CRP= C-reactive protein
eNOS= endothelial cell nitric oxide synthase
HF= heart failure
IL= interleukin
NF-kB= nuclear factor-kappa B
NO= nitric oxide
NPR= natriuretic peptide receptor
NT-proBNP= N-terminal pro brain natriuretic peptide
NYHA= New York Heart Association
PPAR= peroxisome proliferator activated receptor
TNF-α= tumor necrosis factor-α

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ABSTRACT

Adiponectin and brain natriuretic peptide (BNP) are hormones produced by adipocytes and myocardial cells respectively, and have emerged as important diagnostic and prognostic tools in cardiovascular disease. Levels of adiponectin are down-regulated in obese and diabetic individuals and this hormone exhibits favorable effects on atherogenesis, endothelial function and vascular remodeling. On the other hand, BNP and the fragment N-terminal proBNP (NT-proBNP) are natriuretic peptides released from the heart in response to pressure and volume overload and have become diagnostic tools and predictors in several cardiac abnormalities, beyond heart failure. This brief review will discuss the prognostic significance of these two hormones and epidemiological and clinical data from studies will be presented.

INTRODUCTION

Adiponectin and brain natriuretic peptide (BNP) are hormones released from adipocytes and myocardial cells respectively, in response to different stimuli. Adiponectin is the most abundant adipokine secreted by adipose tissue that may couple regulation of insulin sensitivity with energy metabolism.[1] Decreased plasma concentration has been observed in patients with diabetes, metabolic syndrome and coronary artery disease, and this may play a key role in the development of insulin resistance. The exact mechanism underlying anti–inflammatory properties of adiponectin is not yet well understood but there is evidence that its properties may be related, in part, to its ability to stimulate production of nitric oxide (NO), which is considered to be the potent vasodilator substance produced from endothelial cells.[2] Nowadays, adiponectin is increasingly recognized to be both a potential biomarker for the metabolic syndrome and a possible therapeutic target for the treatment of cardiovascular disease.

Brain natriuretic peptide is one of the three major natriuretic peptides, atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP) and C-type natriuretic peptide (CNP), all of which share a common 17-amino-acid ring structure and have cardioprotective actions against volume overload.[3] Although this peptide was called

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brain (B-type) natriuretic peptide (BNP), the primary site of BNP synthesis is the ventricular myocardium.[4] Its initial diagnostic value was attributed in its ability to distinguish heart failure from other causes of dyspnea. Moreover, recently BNP and NT–proBNP have been related to other cardiac diseases, such as stable and unstable angina, valvular heart disease and sudden death, adding a new angle in their diagnostic and prognostic roles. In this review, the prognostic role of adiponectin and BNP in cardiovascular diseases will be briefly presented.

MOLECULAR CHARACTERISTICS AND FUNCTION OF ADIPONECTIN

The adipocyte is an active secretory cell producing several cytokines (adipokines) including tumor necrosis factor-α (TNF-α), interleukins, plasminogen activator inhibitor type 1, leptin and adiponectin.[1] Adiponectin, also called ARCP30, AdipoQ, apM1 and GBP28, is the most abundant adipokine and is increasingly recognized to be both a potential biomarker for the metabolic syndrome and a possible therapeutic target for the treatment of cardiovascular disease in obese patients.[5] It is a 30-kDa protein which was first described in 1995. It consists of an N-terminal collagenous domain and a C-terminal globular domain which has structural similarities to tumor necrosis factor-α (TNF-α).[6,7] The monomers of adiponectin have been shown to aggregate into several polymeric forms in plasma, including trimeric, hexameric and high-molecular weight oligomeric forms. Adiponectin exists in the circulation as a full length protein and a proteolytic smaller globular domain fragment. Plasma adiponectin levels in humans are quite high, normally ranging from 3 to 20 μg/mL and there is a strong negative correlation between plasma levels and body mass index, especially visceral adiposity.[8] The expression of adiponectin in adipose tissue seems to be regulated by several mechanisms via humoral and neuronal pathways. Two adiponectin receptors were identified in 2003, AdipoR1 and AdipoR2.[9] The first, AdipoR1 is a high affinity receptor for the globular C-terminal domain and is expressed mainly in skeletal muscles. On the other hand, AdipoR2 has intermediate affinity for both forms of adiponectin and is most abundant in the liver.[9] T-cadherin is a glycosylphosphatidylinositol (GPI) – anchored extracellular protein and has been demonstrated as a receptor for hexameric and high molecular weight adiponectin but not for trimeric or globular adiponectin.[10] Tissue distribution of T-cadherin is widespread in cardiovascular system, nervous system and muscle but is not highly expressed in the hepatocyte, which is one of the major targets of adiponectin.[11]

There are several conditions and factors that regulate the metabolic function of adiponectin. Thus, insulin and insulin–like growth factor-1 both upregulate adiponectin expression, whereas TNF-a, PPAR-α and PPAR-γ agonists, as metformin and thiazolidinediones respectively, have the opposite effect.[12,13] Angiotensin II also reduces adiponectin production probably via signaling through the angiotensin II type 1 receptor.[14] In addition, sympathetic activation suppresses adiponectin expression via adrenergic β function. Most other factors with a significant impact on adiponectin regulation have inhibitory effects. These include catecholamines, glucocorticoids, cytokines, prolactin, growth hormone and androgens.[15] Adiponectin regulates metabolism and insulin sensitivity, at least in part, by promoting the phosphorylation and activation of AMP-activated protein kinase (AMPK), which is a stress – responsive kinase, in skeletal muscle, liver and adipocytes and affects many aspects of cellular metabolism including glucose uptake, glucose utilization and fatty acid oxidation. AMPK activation is believed to be mediated by adiponectin binding to the cell surface receptors AdipoR1 and AdipoR2.[16]

ADIPONECTIN AND CARDIOVASCULAR DISEASE

Adiponectin may be the most relevant and promising adipokine with respect to a better understanding of the link between obesity and coronary heart disease. Importantly, low levels have been demonstrated in patients with ischemic heart disease (Fig. 1). In a prospective study, men with high adiponectin levels were at lower risk of myocardial infarction than those with lower levels. This association was independent of common risk factors, such as diabetes or hypertension.[17] Additionally, low adiponectin levels were associated with both carotid atherosclerosis and cardiovascular disease.[18] Adiponectin levels have also been reported to rapidly decline after acute myocardial infarction. The protective action of adiponectin against myocardial ischemia appears to be mediated by its

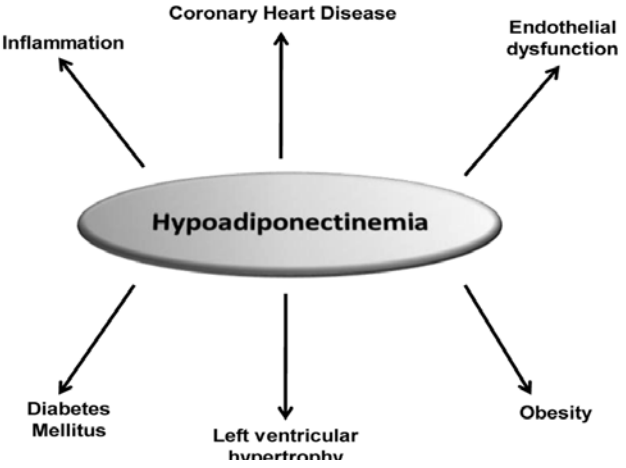

FIGURE 1. Conditions associated with hypoadiponectinemia.

ability to activate cyclooxygenase-2 (COX-2) in cardiac cells which has been shown to play an important cardioprotective role.[19] These studies have additionally demonstrated that hypoadiponectinemia seems to be a negative prognostic indicator for the development of cardiovascular disease especially in obese patients. In patients with acute coronary syndromes, where a vulnerable coronary plaque is known to be the key feature of the pathophysiologic process, plasma concentrations of adiponectin have been found significantly lower than those in patients with stable angina pectoris indicating thus a possible role of adiponectin in maintaining coronary plaque stability.[20] Consistent with this observation, adiponectin levels have been significantly associated with coronary lesion complexity especially in men while they have not proven to be such a good predictor of coronary heart disease in women.[21]

Clinical studies have shown that patients with essential hypertension appear to have significantly lower plasma adiponectin levels than normotensive patients. The underlying mechanism may be involving the effects of angiotensin II. Infusion of angiotensin II in rats decreased plasma adiponectin levels via signaling through the angiotensin II type 1 receptor.[22] Additionally, patients with essential hypertension treated with angiotensin II receptor antagonists or angiotensin – converting enzyme inhibitors, had increased adiponectin concentrations without affecting body mass indices. The positive correlation between adiponectin levels and hypertension has been found more significant in men compared to women.[23] Moreover, hyperadiponectinemia is positively correlated with high-density lipoprotein levels and negatively with triglycerides and apolipoprotein (Apo) B-100. These correlations remain significant even after adjusting for obesity – associated variables.[24] In contrast, low-density lipoprotein and total cholesterol do not have significant independent relationship to adiponectin levels.[25]

Although it is not clear how or whether adiponectin itself has anti–inflammatory properties, it is clear that adiponectin production by adipose tissue can be inhibited by systemic inflammation. Adiponectin production by adipocytes is inhibited by inflammatory cytokines such as TNF-α in vitro and this process may be mediated in part by NF-kB signaling. Thus, adiponectin reduces the TNF-α stimulated expression of adhesion molecules, the expression of the pro-inflammatory cytokine IL-8 in endothelial cells and inhibits the transformation of macrophages to foam cells.[26] On the other hand, adiponectin increases the expression of the anti-inflammatory cytokine IL-10 and the tissue inhibitor of metalloproteinase-1 in macrophages.[27] Moreover, it has been found that expression of adiponectin is inversely associated with that of CRP in men with coronary artery disease.

Adiponectin seems to have beneficial effects in angiogenesis and endothelial function through the AMPK pathway in the vasculature, which has been identified as a regulator of endothelial cell nitric oxide synthase (eNOS) activation as well as a number of cellular responses important for the angiogenesis process.[28] Globular adiponectin increases eNOS both expression and activity in endothelial cells and improves ox-LDL induced suppression of eNOS activity.[29] Further studies have demonstrated the anti-apoptotic action of adiponectin in endothelial cells especially by inhibiting angiotensin II apoptosis in endothelial cells.[30] Moreover, there is evidence that adiponectin promotes directly the formation and growth of new blood vessels stimulating endothelial cell migration and differentiation into capillary – like structures in vitro through activation of AMPK signaling pathway.[28] In vascular lesions, adiponectin seems to suppress the proliferation of smooth muscle cells promoting vascular remodeling. In vitro studies have shown that adiponectin can inhibit the proliferation and direct migration of smooth muscle cells to platelet – derived growth factor – BB ameliorating this way the neointimal hyperplasia and proliferation following acute vascular injury.[31] These results are consistent with in vivo animal studies where adiponectin knockout mice showed an accelerated thrombus formation on carotid arterial injury with a He-Ne laser.

SYNTHESIS AND FUNCTION OF BRAIN NATRIURETIC PEPTIDE (BNP)

The brain natriuretic peptide (BNP) is synthesized in bursts as a preprohormone of 134 residues and constitutively released from ventricular myocytes when left ventricular wall stress increase. Then it is cleaved to yield a 108-amino-acid prohormone, which is further cleaved by an unknown protease into an inactive 76 aminoacid N-terminal fragment (NT-proBNP) and a 32 aminoacid active hormone (BNP). It must be noticed that BNP gene expression can be increased very rapidly in response to an appropriate stimulus such as tachycardia, glucocorticoids, thyroid hormones and vasoactive peptides angiotensisn II and endothelin-1, independent of their hemodynamic effects (Fig. 2). BNP has a half-life of approximately 20 min, while the half-life of the more stable NT-proBNP is about 120 min.[3,4] Normal plasma levels of BNP and NT-proBNP vary widely and depend on both age and gender. For BNP, they range from a few picograms per milliliter in young males to higher than 100 pg/ml in apparently healthy females over 70 years old. For acutely dyspneic patients, some have suggested cutoffs of BNP <100 pg/ml and NT-proBNP <300 pg/ml to rule out heart failure. The biological actions of BNP are mediated through membrane – bound natriuretic peptide receptors A (NPRs-A) that are linked to a cyclic guanosine monophosphate – dependent signaling cascade. NT-proBNP is eliminated mainly through kidney clearance, while BNP is mostly eliminated either through binding to its receptors NPRs-A or via degradation by neutral endopeptidase that is present on the surface of endothelial cells. However, renal failure is associated with elevations in both BNP and NT-proBNP levels. In general,

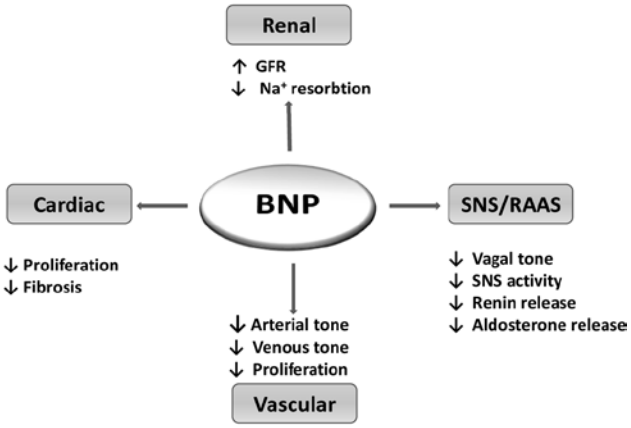

FIGURE 2. Effects of Brain Natriuretic Peptide (BNP).

BNP and NT-proBNP are reasonably correlated and both of them can be used in the routine clinical practice accordingly to each clinician's decision.

BNP AS PROGNOSTIC BIOMARKER FOR CARDIOVASCULAR DISEASE

Both BNP and NT-proBNP can predict death and cardiovascular events in patients presenting with acute or chronic heart failure (HF) and they are being studied as a possible screening tool.[3] It must be noted that pooled results from five studies showed that a BNP increase of 100 pg per mL was associated with a 35% increase in risk of death.[32] BNP was the only statistically significant independent predictor of mortality in nine studies, indicating that BNP tests potentially are more useful than traditional predictors of mortality (e.g., age, ischemic etiology, left ventricular ejection fraction, NYHA classification, serum creatinine levels).[32] Data from the multicenter prospective study REDHOT (Rapid ED Heart Failure Outpatient Trial) showed that in patients with HF admitted to emergency department, BNP was predictive of future HF events and mortality and outperformed physician assessment, which had a poor predictive value.[33] Moreover, the response of plasma BNP to therapy was illustrated in a study enrolling 102 patients with severe HF who were studied at baseline and three months after optimized treatment including ACE inhibitors, beta blockers and digoxin. Optimized therapy was associated with significant reductions in plasma BNP (917 at baseline to 285 pg/mL) as well as in other neurohumoral factors such as norepinephrine.[34] Additionally, data from Val–HeFT (Valsartan Heart Failure Trial) indicate that in 4300 patients with congestive HF, those with the greatest increase in BNP despite medical therapy had the highest morbidity and mortality.[35] Moreover, several studies have indicated the usefulness of BNP in predicting the risk of sudden death. Particularly, in 452 patients with severe left ventricular dysfunction (ejection fraction <35%) only 1% of patients with BNP <130 pg/mL died suddenly compared with 19% of patients with BNP ≥130 pg/mL.[36] In addition, in multivariate analyses BNP was more closely associated with mortality than was NYHA class or left ventricular ejection fraction. It must be noted that BNP, beyond its relationship to sudden cardiac death, may be also associated with re-hospitalizations, a setting in which traditional risk factors do not have any prognostic value. Furthermore, it is known that plasma BNP and NT-proBNP levels are lower in obese patients but despite this phenomenon, plasma BNP retains its prognostic value in this group of patients.[37]

Although natriuretic peptides BNP and NT-proBNP most often are used in patients with dyspnea and those with established HF, their plasma concentrations have been implicated as predicting markers in a variety of other cardiac diseases. Thereby, acute coronary syndromes have been associated with a rise in BNP and NT-proBNP levels even in the absence of concomitant heart failure. The degree of elevation might reflect the severity of left ventricular dysfunction.[38] In a study that enrolled 1085 patients with stable coronary artery disease for a mean follow up about 2.5 years, BNP and ejection fraction were the strongest predictors of future events, independent of known risk factors. Plasma NT-proBNP appears to have equivalent predictive value in these patients.[39] In the AtheroGene study data provided independent evidence that BNP was a strong predictor of cardiovascular risk in patients with stable angina independent of left ventricular systolic performance and known risk factors.[40]

The prognosting importance of plasma BNP in patients presenting with acute coronary syndromes was best illustrated in a study of 2525 patients with unstable angina and non-ST elevation myocardial infarction in whom plasma BNP was measured about 40 hours after the onset of symptoms. After adjusting for other predictors of risk, such as renal function, electrocardiographic changes, and troponin I levels, BNP was reputedly capable to assess the long-term risk of death and nonfatal cardiac events across the spectrum of acute coronary syndromes.[41] Furthermore, persistent elevation of NT-proBNP 3 to 6 months after an acute coronary syndrome has been associated with impaired left ventricular function. Moreover, in a study that enrolled 4266 patients with acute coronary syndrome, those with elevated levels of BNP at study entry and with BNP levels lower than 80 pg/mL at 4 months tended to have only modestly increased risk (HR 1.7; 95% CI, 1.0-2.9) compared with patients with BNP levels lower than 80 pg/mL at both visits.[42] The largest study of NT-proBNP in acute coronary syndromes comes from the analysis of data on 6809 patients presented with non-ST elevation myocardial infarction, in the GUSTO IV ACS trial. According to this analysis, NT-proBNP illustrated a stronger correlation with mortality than any other marker studied, including cTnT and CRP. In this study, patients within 24 hours of symptom onset

with NT-proBNP values ≤98 ng/L had a significantly lower mortality rate at one year than those with values ≥4634 ng/L.[43]

Natriuretic peptides have been considered a useful clinical tool for monitoring patients suffering from valvular disease before and after surgery. Raised levels of BNP and NT-proBNP have been positively correlated with the severity of valvular disease. In particular, among patients with aortic stenosis these peptides may be a useful adjunct to classify patients with equivocal symptoms who are at risk for rapid progression.[44] In patients who undergo surgical valve replacement or conservative management, natriuretic peptides levels might predict survival and postoperative left ventricular function. Also, there has been shown a significantly positive correlation between low levels of BNP and the risk of postoperative atrial fibrillation.[46] In chronic aortic regurgitation, BNP levels tend to rise less than in aortic stenosis even when left ventricular dilatation has occurred.[47] With respect to mitral valve disorders, BNP was shown to be a marker of poor outcome in a study of 124 patients with mitral regurgitation, where levels were independently predictive of death.[48]

CONCLUSIONS

Adiponectin and BNP are targets for future research as prognostic markers of morbidity and mortality in several cardiovascular diseases. Interventions increasing adiponectin levels are weight loss and the administration of insulin sensitizers, such as thiazolidinediones. More research is needed in this field as well. As we mentioned above, the beneficial effects of adiponectin in the atherosclerosis cascade and the development of cardiovascular disease are not completely undrerstood and future research is needed to clarify its pathophysiologic role.

On the other hand, BNP levels increase in several conditions affecting left ventricular function, so their measurement, especially in asymptomatic patients, might be a useful clinical tool even for the primary care physician. It is expected that within the next few years BNP and NT-proBNP will find clinical application not only in the assessment of the severity and the progression rate of heart failure, but also of other cardiovascular diseases such as unstable angina and valvular heart disease. The major limitation for using BNP as a prognostic biomarker is that specific therapeutic strategies for patients with raised concentrations have not yet been widely available.

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