Clinical use of adiponectin as a marker of metabolic dysregulation

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Adiponectin concentrations exhibit strong cross-sectional relationships with obesity, inflammation, and diabetes. Adiponectin concentrations have been extensively evaluated as epidemiologic markers of diabetes and cardiovascular disease risk. In the present review we will provide an overview of these epidemiologic relationships as the backdrop for an evaluation of the clinical applications of adiponectin measurements. These include using adiponectin as an indicator of need for preventive or therapeutic intervention, as a predictor of response to therapy, and as a marker of therapeutic effectiveness. These efforts are laying the groundwork for the transition of adiponectin measurements from the laboratory to the clinic.

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\section*{Introduction}

The discovery of adiponectin has proven to be a watershed moment in the study of obesity and associated disorders. Adiponectin circulates in high concentrations and is readily quantitated using accessible methodologies. In contrast to all other adipose-derived circulating factors, adiponectin has the epidemiologically interesting but as yet unexplained feature of circulating in lower concentrations in proportion to the degree of obesity. At present it appears that factors that determine the overall concentration are distinct from the factors that reduce the concentration in relation to degree of obesity and metabolic dysfunction. The body of epidemiologic data that will be reviewed here is based on the observation of reduced adiponectin concentration in proportion to metabolic dysfunction; data exploring this broader phenomenon will be highlighted where possible.
Adiponectin circulates as in a variety of forms, including low-molecular weight and high molecular weight subtypes (representing differing numbers of monomers aggregated into circulating complexes). While the main body of adiponectin epidemiology has used measures of total circulating adiponectin, associations with adiponectin molecular weight subtypes have also been explored.

The current manuscript is not intended as a comprehensive summary of the literature on each of the points discussed below, but rather uses prominent examples from the literature to support specific statements. A qualitative summary of the data supporting each particular use of adiponectin measures is provided in Table 1. These are discussed in detail in the following sections.

**Adiponectin as a marker of metabolic dysfunction**

Adiponectin concentrations are strongly determined by obesity status. However, adiponectin is also associated with measures of insulin resistance, markers of inflammation and markers of immune activation, and on this basis adiponectin has been presented as reflecting these features of obesity in epidemiologic evaluations. These features are of course inter-related and at present there is no sufficient evidence to distinguish associations of adiponectin with immunologic or inflammatory factors from the core mutual association of these factors with obesity.

**Adiponectin as a marker of metabolic status**

**Obesity**

In adults and in children, adiponectin concentrations are inversely associated with obesity [1–4]. This is a modifiable aspect of obesity, since reduction of obesity through a variety of interventions produces concordant increases in adiponectin concentrations [1,2,5–8]. Improvements in adiponectin have also been reported with targeted dietary interventions that do not induce weight loss [9]. In a minority of reports weight loss failed to increase adiponectin concentrations [10,11]. Changes in adiponectin with weight loss have some specificity to the fat depot that is mobilized, with interesting differences in particular between subcutaneous fat removal and loss of visceral or whole-body fat content [12]. Overall it appears that adiponectin concentrations can be improved following reductions in weight achieved through diet, exercise, medications and surgery, with interesting but minor differences in the fat depot specificity of the responses.

**Insulin resistance**

Inverse associations of adiponectin concentrations with simple fasting indices of insulin resistance have been consistently demonstrable in adult populations [13,14] and in pediatric populations [3,4]. The high molecular weight fraction was statistically superior to total adiponectin concentrations in its

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association with homeostasis model assessment (HOMA) in a large population of Japanese subjects [15]. Where the adiponectin/leptin ratio has been evaluated, the associations are numerically improved but not practically different from associations with total adiponectin alone [16].

In the case of rare diseases of the insulin receptor system, adiponectin levels can be discordant with insulin resistance. In affected individuals adiponectin concentrations are paradoxically elevated despite profound resistance to the glycemic effects of insulin, and in this instance adiponectin concentrations can be diagnostically useful [17].

**Inflammation**

Adiponectin concentrations are inversely associated with markers of inflammation [3,18]. Emerging molecular evidence suggests that effects of adiponectin on monocytes as a component of regulation of inflammation may be separable from effects of adiponectin on insulin resistance [19]. In some analyses adiponectin concentrations associate more strongly with measures of inflammatory status than with measures of insulin resistance [20] whereas in other reports adiponectin is most potently associated with measures of insulin resistance even when inflammatory measures are concurrently evaluated [18].

Exercise-induced and pharmacologically-induced weight loss produces concurrent improvements in inflammatory markers and adiponectin [1,2,21–23]. The relative change in high molecular weight adiponectin following weight loss appears to be superior to the relative change in total adiponectin following diet intervention, suggesting a venue where the distinction of molecular subtypes may be of value [24]. Therapies that directly target inflammation have been found to concurrently increase adiponectin concentrations, independent of any effect on body weight. For example, etanercept, a monoclonal antibody against the tumor necrosis factor alpha receptor, reduces C-reactive protein concentrations and concurrently raises adiponectin concentrations in patients with obesity and the metabolic syndrome [25]. Such observations demonstrate that inflammation and adiponectin are linked through biological mechanisms that are at least partially independent of obesity. The mechanisms connecting adiponectin with inflammation in obesity likely include such direct mechanisms plus other obesity-specific mechanisms.

**Diabetes mellitus**

Adiponectin concentrations are reduced in individuals with type 2 diabetes, and in individuals with prediabetic states of dysglycemia [7]. This relationship appears to be at least partially explained by the presence of obesity in these groups. The severity of dysglycemia in type 2 diabetes may associate inversely with adiponectin concentrations [26], such that adiponectin concentrations have been suggested as a potential clinical marker of therapeutic effectiveness (explored in detail below).

In subjects with type 1 diabetes there does not appear to be a relationship between glycemic status and adiponectin concentrations independent of obesity [27]. Adiponectin concentrations are elevated in type 1 diabetes [28], and also exhibit a direct (not inverse) association of duration of type 1 diabetes with adiponectin concentrations, independent of adiposity [29]. The prevalence and incidence of microvascular disease in type 1 diabetes was also directly related to adiponectin concentrations [30]. Further, in type 1 diabetes adiponectin concentrations are directly associated with all-cause and cardiovascular mortality rates [31]. The association of adiponectin with heart disease risk in type 1 diabetes is variably reported as inversely [32] or directly [33] associated with baseline adiponectin concentrations.

**Adiponectin as a marker of disease risk**

**Adiponectin and diabetes risk**

In the Diabetes Prevention Program, baseline adiponectin concentrations were strongly inversely associated with risk of progression to overt type 2 diabetes, even after adjustment for obesity, age, sex, and traditional dysglycemic predictors of diabetes risk [7]. Similar results have been reported in other populations evaluating prospective diabetes incidence [34,35]. Analyses from the MONICA/KORAS study...
suggested that mathematical combinations with leptin measurements may further augment the discriminatory power of adiponectin for diabetes risk assessment [34]. Little work has been done to establish comparative potency of adiponectin subtypes versus total adiponectin in assessing diabetes risk [36].

The use of adiponectin as a biomarker for diabetes risk in the context of other risk factors has been quantitatively evaluated. In a large Chinese population, clinical predictors (age, sex, family history of diabetes, smoking, physical activity, hypertension, waist circumference, fasting glucose and dyslipidemia) alone produced a Receiver Operator Characteristics (ROC) area under the curve of 0.802. Adding a 2 h oral glucose tolerance test (OGTT) glucose reading significantly improved this clinical predictor AUC to 0.852. Adding adiponectin plus circulating TNF receptor 2 (TNFr2) concentrations to the clinical predictors improved the area under curve (AUC) to 0.830, significantly greater than the clinical predictors alone and not statistically different from the model including the OGTT value [37]. Adiponectin concentrations, together with a collection of related biomarkers, statistically improved the capacity of the FINDRISC score to identify subjects with undiagnosed diabetes (ROC AUC 0.772 vs 0.727). A similar approach in the Inter99 cohort found that a biomarker risk score including adiponectin produced a superior ROC AUC versus traditional glucose criteria or traditional clinical criteria [38]. Using other metrics of incremental discriminatory power in a discovery/validation paradigm using two large prospective datasets, adding adiponectin along with other emerging risk factors to traditional risk predictors produced significant improvements in diabetes prediction (improved discriminant index and net reclassification index) [39]. The Diabetes Risk Score, developed in a Caucasian population, incorporates adiponectin concentration with other biomarkers and with traditional clinical diabetes risk predictors. This score improved the ROC AUC for diabetes incidence and produced a significant reclassification index in the IRAS population [40].

These observations suggest that adiponectin concentration provides a useful surrogate of risk of progression to type 2 diabetes among at-risk individuals. This could be of value in screening and interventions for diabetes prevention in clinical populations, but is also of value in clinical trials. These uses are only beginning to emerge. For example, a study of selenium supplementation in British individuals used adiponectin concentrations to assess the effects of the intervention to alter diabetes risk [41].

Adiponectin and cardiovascular disease risk

Adiponectin concentrations are inversely associated with cardiovascular disease incidence in most [42–44] but not all [45] the populations studied. In the Physicians’ Health Study the inverse relationship of total adiponectin with incident coronary heart disease (CHD) was robust to adjustment for traditional CHD risk factors [43].

The leptin/adiponectin ratio and the ratio of HMW to total adiponectin were predictive of incident cardiovascular disease (CVD) [46,47]. Similarly, high molecular weight (HMW) but not total adiponectin concentrations predicted incident myocardial infarction in non-diabetic men [48]. Adiponectin concentrations are inversely associated with prevalence and severity of angiographically determined cardiovascular disease [49,50]. High molecular weight adiponectin concentrations and the HMW/total adiponectin ratio were strongly correlated with extent and severity of angiographically determined coronary artery disease [51].

Adiponectin concentrations increase with aging, a phenomenon that is separate from the persisting inverse relationship with obesity. The prospective relationships between adiponectin and future CVD in the Rancho Bernardo study of aging was complex, with some direct and some inverse associations by subgroups [52]. In a prospective study of British participants aged 60–79 years, followed for an average of 9 years, higher adiponectin concentration was directly associated with greater CVD risk and mortality [53]. These observations suggest that there is a complex mixture of a direct relationship between adiponectin and age-related CVD risk plus the general paradigm of an inverse relationship of adiponectin with obesity/dysmetabolic state-associated CVD risk.

Total adiponectin concentrations were modestly inversely predictive of stroke incidence in subjects aged 70–82 at baseline [54], but in other populations the association of stroke incidence with adiponectin was not seen [55]. In the Women’s Health Initiative HMW adiponectin associated with CVD risk factors, but it was not prospectively associated with stroke risk [56].
In congestive heart failure adiponectin concentrations are directly (not inversely) related with severity of contractile dysfunction [57–59], and with mortality [57,59]. In the Framingham Offspring Study, when adjusted for other risk factors, adiponectin was not associated with prospective risk of new congestive heart failure [60].

In aggregate, these observations suggest that there is promise for the application of adiponectin and other adipokines as a measure of atherosclerotic heart disease risk. However, these associations are more complex than the relationship of adiponectin with diabetes risk. It would appear that using adiponectin as a predictor of CVD risk in clinical trial or health care circumstances would require a more complete understanding of how adiponectin is serving as a marker for competing risks and competing disease states.

Adiponectin and mortality risk

In subjects with coronary artery disease, adiponectin concentrations were directly associated with total mortality [61,62]. As noted above, a prospective study of British participants aged 60–79 years, followed for an average of 9 years, found that higher adiponectin concentration were associated with greater mortality [53]. In subjects with peripheral arterial disease, adiponectin concentrations were again directly associated with all-cause mortality, an effect that persisted after adjustment for concurrent obesity-related mortality risk factors [63]. In congestive heart failure adiponectin concentrations are directly related with mortality [57,59,64]. And among non-obese subjects with congestive heart failure, total adiponectin but not HMW adiponectin was associated with mortality [65].

It appears that adiponectin concentrations are determined in part by renal status, with higher concentrations in individuals with worsening albuminuria [66] and with decreasing glomerular filtration rate [67]. Nevertheless, hypoadiponectinemia is a marker of all-cause and cardiovascular mortality in patients with renal disease, through interactions with leptin and waist circumference [68]. Similarly, in non-diabetic dialysis patients, hypoadiponectinemia predicted increased mortality [69]. Conflicting data exist, complicating our understanding of these relationships [70].

These relationships of adiponectin concentrations with mortality risk do not uniformly follow the pattern that would be expected if adiponectin were simply reflecting obesity or dysmetabolic status-associated risk. This hints at an underlying relationship of adiponectin with other factors that contribute to mortality risk, and argues against the use of adiponectin as a marker of obesity-associated mortality risk. An increased understanding of this relationship could, however, result in adiponectin being of use as a marker for mortality risk associated with other factors.

Clinical use of adiponectin measurements

Using adiponectin to assess need for therapy

The use of adiponectin as a tool to assess disease risk was reviewed above. Overall, this application has not yet spread beyond use in clinical trials. Nevertheless the potential exists to use a baseline adiponectin measurement to decide whether to intervene for diabetes or CVD prevention in an individual. To our knowledge, no systematic studies of these uses have been published.

Healthy children of diabetic pregnancies have adverse cardiometabolic biomarker profiles compared to otherwise matched children from non-diabetic pregnancies, including a lower adiponectin concentration at matched body weights [71]. Adults who were low-birth weight babies have lower circulating adiponectin concentrations than matched controls [72]. These observations have interesting implications for metabolic programming effects of intrauterine exposures. However, there are no data to inform moving from this knowledge to making recommendations for therapeutic interventions at any stage in the life cycle of affected individuals.

Using adiponectin to choose among therapies

Changes in adiponectin concentrations can be used as a biomarker indicating risk reduction with therapy (use of adiponectin as a specific measurement of response to therapy is addressed below).
Adiponectin has been used in this way as a surrogate marker of anticipated beneficial effects of adiponectin on vascular status. For example, effects of therapy with statins on adiponectin concentrations have been proposed to serve as an indicator of anti-inflammatory actions [73,74], although some studies argue against this application [75]. Similarly, effects on adiponectin concentrations have been used to compare the additive metabolic benefits of antihypertensive agents [76]. In the Diabetes Prevention Program, favorable effects of randomized therapies on a number of biomarkers including adiponectin have been interpreted as potentially reflecting treatment-associated reductions in CVD risk [77].

**Adiponectin as a marker of therapeutic success**

Change in adiponectin has been proposed as a clinical measure of efficacy of therapeutic interventions in dysmetabolic patients [78]. In the Diabetes Prevention Program, the therapeutic benefit of the metformin therapy and of the lifestyle intervention was associated with the change in adiponectin concentrations [7]. In this context adiponectin concentrations can be interpreted as reflecting the diabetes prevention benefit of therapy.

Change in adiponectin concentrations can also reflect metabolic benefits of diabetes therapies. In a study adding the sulfonylurea glibenclamide versus the alpha-glucosidase inhibitor acarbose to background metformin therapy, the clinical efficacy of acarbose was greater than glibenclamide and the acarbose effects included a statistically significant increase in circulating adiponectin concentrations [79]. In a separate placebo-controlled study of acarbose in type 2 diabetes, after 3 months of treatment adiponectin concentrations were significantly increased [80], but not all studies show this effect of acarbose [81]. In a small study, neither metformin or repaglinide produced significant changes in adiponectin concentrations despite a significant weight benefit of metformin [82]. Agents in the peroxisome proliferator-activated receptor gamma (PPARgamma) class, while undeniably effective for glucose control have been found to produce adverse effects which have reduced enthusiasm for the class. Nevertheless diabetes therapy with agents in this class consistently produced improvements in adiponectin concentrations [83]. In elderly subjects, improvement in insulin resistance following treatment with glimepiride was most strongly associated with concurrent changes in adiponectin concentrations [84], although effects of sulfonylureas on insulin resistance are not generally observed. In diabetes, acute improvements in glycemic control with insulin produce concordant increases in adiponectin concentrations [85].

Antihypertensive agents can also affect adiponectin concentrations, through unexplained mechanisms. Increased circulating adiponectin has been observed with mineralocorticoid receptor blockade [86] without concurrent changes in obesity, potentially providing a blood pressure-independent marker of therapeutic benefit with this class of antihypertensive agents [86]. Agents that are antagonists to the renin–angiotensin system have been found to increase adiponectin in hypertensive subjects with insulin resistance [87], metabolic syndrome [88], or diabetes [89]. A parallel effect was seen with the calcium channel blocker nifedipine [90] and with the beta-adrenergic receptor antagonist nebivolol [91].

In congestive heart failure, response to therapy with the beta adrenergic receptor antagonist carvedilol was associated with reductions in adiponectin concentrations [92]. In acute congestive heart failure, in contrast, therapy with the Atrial Natriuretic Factor (ANF) agonist carperitide produced an increase in circulating adiponectin concentrations in proportion to the beneficial functional response to therapy [93]. Although the directionality of these changes is opposite to what is expected in dysmetabolic states, the underlying relationships in congestive heart failure (CHF) are altered as detailed above, so a particular change effect must be carefully interpreted.

Coronary artery revascularization increases adiponectin concentrations [94], and following coronary artery stenting, the residual stenosis at 6 months was inversely associated with increases in circulating adiponectin concentrations [95]. However, one study reports increased adiponectin concentration following revascularization [96]. Peripheral revascularization success was also inversely related to baseline adiponectin concentrations among subjects with critical limb ischemia [97]. And regression of angiographically determined coronary arterial plaques following statin therapy was associated with an increase in adiponectin concentrations [74]. In a prospective observational study the
traditional major atherosclerotic cardiac event (MACE) outcome following bypass surgery versus medical therapy was inversely associated with adiponectin concentrations, leading to a suggestion that adiponectin could be used to choose between therapies for cardiovascular disease [98]. However, adiponectin and related biomarkers have not been subjected to rigorous clinical studies evaluating adiponectin-based strategies to choose among cardiovascular interventions.

**Adiponectin as a therapeutic?**

In animal studies adiponectin's direct effects are evaluated using genetic tools (e.g. adiponectin deficiency), using adenovirus-delivered inducible overexpression, or using minipump infusion of manufactured adiponectin. Using these techniques, adiponectin has been shown to have anti-inflammatory and anti-atherosclerotic benefits [99,100]. There is clearly therapeutic potential for treatments that directly deliver adiponectin or adiponectin mimetics [101], but the molecular complexities of adiponectin have precluded its production as a therapeutic agent to date. To our knowledge there are currently no adiponectin-mimetic therapies available for clinical testing. At present, vascular therapies and metabolic interventions can be identified that have effects on adiponectin as a component of their integrated action, and these effects may be contributing to the identified clinical benefits. But determining the direct effects of adiponectin on these outcomes remains a challenge for the future.

**Emerging applications**

Adiponectin was discovered as a fat-derived hormone, and the majority of work has evaluated adiponectin in the context of metabolic and vascular biology. However a number of novel applications have emerged. We will present two examples of interest.

In 40 Japanese women with Type 2 diabetes, adiponectin concentrations were associated with bone mineral density (BMD) determined by dual energy X-ray absorptiometry (DEXA) [102]. In a separate dataset of 81 postmenopausal women without diabetes adiponectin concentrations associated with circulating markers of bone health such as osteoprotegerin [103]. Separately, adiponectin was directly associated with circulating concentrations of osteocalcin [104]. These observations suggest that adiponectin may be of use in epidemiologic studies of bone health, but may also indicate a previously unappreciated contribution of adiponectin to bone biology.

Despite the complexities of manufacturing adiponectin complexes as a biologic therapy, the monomeric globular head is amenable to production using established techniques. One novel application of this adiponectin subtype is in molecular imaging, where adiponectin-labeled nanoparticles have undergone preliminary evaluation as a potential imaging marker for atherosclerotic burden [105].

**Summary**

The clinical utility of adiponectin is based on its strong epidemiologic relationships with obesity, inflammation, and diabetes, strengthened by its established biological actions in the vasculature and on immune cells. Adiponectin concentrations have been extensively evaluated as epidemiologic markers of diabetes and cardiovascular disease risk. And increasingly adiponectin concentrations are being evaluated as indicators of need for therapy, predictors of response to therapy, and markers of therapeutic effectiveness. These efforts are laying the groundwork for the transition of adiponectin measurements from the laboratory to the clinic.

**Practice points**

- Adiponectin levels are inversely related to weight, but also affected by age and sex.
- Adiponectin levels predict diabetes and cardiovascular disease risk.
- Adiponectin levels change with weight loss and with pharmacologic therapies, providing a potential marker of changes in disease risk with those therapies.
Research agenda

Use of adiponectin as a component of diabetes and cardiovascular disease risk assessment in clinical settings requires further validation and research on how best to implement.

More data are needed to support the application of adiponectin as a component of disease management decision-making.

Prospective studies are needed to analyze changes in adiponectin concentrations as indicators of change in disease risk.

References


