PERSPECTIVES IN DIABETES

The Adiponectin Paradox for All-Cause and Cardiovascular Mortality

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Basic science studies have shown beneficial effects of adiponectin on glucose homeostasis, chronic low-grade inflammation, apoptosis, oxidative stress, and atherosclerotic processes, so this molecule usually has been considered a salutary adipokine. It was therefore quite unexpected that large prospective human studies suggested that adiponectin is simply a marker of glucose homeostasis, with no direct favorable effect on the risk of type 2 diabetes and cardiovascular disease. But even more unforeseen were data addressing the role of adiponectin on the risk of death. In fact, a positive, rather than the expected negative, relationship was reported between adiponectin and mortality rate across many clinical conditions, comprising diabetes. The biology underlying this paradox is unknown. Several explanations have been proposed, including adiponectin resistance and the confounding role of natriuretic peptides. In addition, preliminary genetic evidence speaks in favor of a direct role of adiponectin in increasing the risk of death. However, none of these hypotheses are based on robust data, so further efforts are needed to unravel the elusive role of adiponectin on cardiometabolic health and, most important, its paradoxical association with mortality rate.

Diabetes is one of the most challenging global health problems, affecting an estimated 415 million people worldwide (1). The increased mortality rate observed in patients with diabetes (2), especially those with type 2 diabetes, contributes substantially to the heavy burden that the disease exerts on patients and their relatives and the entire society, with an annual economic cost that in the U.S. alone approximates $100 billion (1).

Discovering novel biomarkers able to predict the risk of mortality in patients with diabetes and furthering the understanding of their mechanisms may help in tackling such a tremendous burden.

Notably, there are no diabetes-specific death-predicting markers. This indicates that though being possibly exacerbated and certainly more prevalent in individuals with versus without diabetes, the mechanisms underlying mortality rate are not different across the two groups. Thus, when addressing the architecture of high mortality risk associated with diabetes, one should really look at molecules, pathways, and pathogenic scenarios that are shared by the general population and presumably several other clinical conditions.

It is now established that processes related to intermediate metabolism, low-grade inflammation, and atherosclerosis are instrumental in shaping the risk of mortality. So, it is not surprising that several adipokines controlling most of the above-mentioned processes do influence mortality rate (3). Among these is adiponectin, a 244 amino acid protein abundantly present in serum (3).

The major aim of this article is to acquaint the readers with the counterintuitive and therefore unexpected relationship between circulating adiponectin levels and mortality rate that has emerged in recent years. In fact, it will be reported and discussed how, despite the well-recognized role of adiponectin as insulin-sensitizing, anti-inflammatory, and cardioprotective factor in cellular and animal models, a direct association between serum adiponectin and mortality rate has been repeatedly and almost uniformly reported within several clinical settings, including diabetes. Although the intimate mechanisms of such paradox are not yet known, some hypotheses, based on intriguing preliminary evidences, will be offered. Finally, we will propose a frame that may help in designing and conducting future studies aimed at better understanding the adiponectin paradoxical association with increased mortality risk.

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BASIC SCIENCE EVIDENCE OF ADIPONECTIN'S BENEFICIAL ROLE ON CARDIOMETABOLIC TRAITS

After posttranslational modifications, adiponectin circulates in trimeric, hexameric, and multimeric high–molecular weight (HMW) isoforms, each activating different signal transduction pathways and possibly leading to distinct biological functions (3). Levels of all circulating adiponectin isoforms are 30–80% heritable, suggesting that they are, at least partly, under genetic control. The *ADIPOQ* gene in chromosome 3q27 and several other loci has been reported by genome-wide association studies (GWAS) to associate with serum adiponectin (4–6).

Adiponectin acts through at least two receptors, AdipoR1 and AdipoR2, which show different binding affinity for globular and full-length adiponectin. AdipoR1 is ubiquitously expressed, whereas AdipoR2 is mostly expressed in white adipose tissue and liver (7). Adiponectin through adenosine 5′-monophospate–activated protein kinase or peroxisome proliferator–activated receptor α activation inhibits gluconeogenesis and stimulates glucose uptake (7).

Besides the effects on glucose metabolism, adiponectin has been also indicated as a cardioprotective molecule by several in vitro studies (8–10). In fact, adiponectin plays a beneficial role on low-grade inflammation by suppressing the expression of IL-8 in tumor necrosis factor α (TNFα)-stimulated human aortic endothelial cells (8). It also suppresses the expression of TNFα and monocyte chemoattractant protein 1 in several cell types (including human circulating monocyte-derived macrophages, stromal vascular fraction cells from human subcutaneous fat pads, and murine alveolar macrophages [9]) and of vascular cell adhesion molecule 1 and TNFα in atherosclerotic lesions of apoE-deficient mice (10). Conversely, in human monocyte-derived macrophages, adiponectin enhances the expression of anti-inflammatory cytokine IL-10 (11). In a mice model with targeted activation of caspase-8, adiponectin exerts antiapoptotic effects in primary neonatal ventricular cardiac myocytes (12), whereas in *db/db* mouse aortic endothelial cells it mitigates oxidative stress by increasing nitric oxide bioavailability through adenosine 5′-monophospate–activated protein kinase and protein kinase A (13). In addition, adiponectin exerts a protective effect on glomerular podocytes by significantly restoring their foot processes in adiponectin knockout mice (14). Finally, through the marked downregulation of scavenger receptor A, adiponectin suppresses the transformation of human monocytes-derived macrophages into foam cells, thus inhibiting the development of atherosclerotic plaques (15).

Although addressing different cell types from different species as well as different pathways possibly involved in atherosclerosis, these studies draw a picture indicating adiponectin as a beneficial molecule for the vasculature, the heart, and, in general, cardiometabolic health.

In the specific context of the adiponectin cardioprotective effect, a significant role seems to be played by T-cadherin identified in C2C12 myoblasts and rodent skeletal muscle as a specific cell membrane binding protein for HWM adiponectin (16). Notably, T-cadherin, which is encoded by the *CDH13* gene, is highly expressed throughout the vasculature, including endothelial cells, smooth muscle cells, and pericytes (17). The role of T-cadherin is critical for cardiovascular protection in several mice models (18,19), with binding to adiponectin mitigating stress-induced cardiac remodeling (18), mediating revascularization after hind limb ischemia (19), and protecting against neointimal and atherosclerotic plaque formation (20).

RELATIONSHIP BETWEEN ADIPONECTIN AND CARDIOMETABOLIC TRAITS

On the basis of the above-reported properties unraveled by basic science studies, it would be conceivable to hypothesize that adiponectin exerts beneficial effects on metabolic and cardiovascular traits in human beings. In fact, in pioneering cross-sectional studies carried out in Pima Indians, circulating adiponectin levels correlated positively with both skeletal muscle (21) and liver (22) insulin sensitivity. In addition, in this same population, adiponectin was negatively correlated with inflammatory markers (23). Along the same line is the observation that insulin-sensitizing agents increase adiponectin concentrations in humans (24). In addition, a prospective study has also shown that low plasma adiponectin concentration predicts the deterioration of insulin sensitivity over time (25).

Unfortunately, the observational design of all such studies could not address whether the reported associations were due to a positive effect of adiponectin on insulin sensitivity. In this regard, it must be considered that subjects with severe insulin resistance due to insulin receptor genetic abnormalities are characterized by increased circulating adiponectin levels (26); in addition, exogenous insulin administration reduces adiponectin levels in healthy individuals (27). Taken together, these two studies (26,27) suggest that insulin is able to decrease circulating adiponectin levels, and therefore it becomes not clear how to interpret the relationship between hypoadiponectinemia and common forms of insulin resistance and hyperinsulinemia reported by epidemiological observational studies (21,22,25,28).

Genetic studies may help cope with similar elusive interpretations on the relationship between a given intermediate trait and an outcome of interest. In fact, if genetic variants robustly affecting the trait are available, their association with the outcome is used to speak in favor of causality. This approach, named as Mendelian randomization (29), has been used to address the relationship between low adiponectin and insulin resistance, giving, unfortunately, ambiguous results (30,31). On one hand, it has been reported that a genetic score including variants in the *ADIPOQ* locus was strongly and directly associated with both high serum adiponectin levels and increased insulin sensitivity at euglycemic-hyperinsulinemic glucose clamp, suggesting that adiponectin does increase insulin sensitivity (30). On the other hand, in a second larger study a genetic score also built on *ADIPOQ* variants showed no association with higher fasting

Table 1—Studies on the association between circulating adiponectin levels and all-cause mortality

First author, year (ref.)	Study population	Subjects (n)	Deaths (n)	Adiponectin-mortality association
Efstathiou, 2005 (65)	Ischemic stroke	160	85	↓
Kistorp, 2005 (66)	Chronic heart failure	195	46	↑
Pilz, 2006 (67)	General population (78.6% with coronary artery disease)	3,146	482	↑
Cavusoglu, 2006 (68)	General population	325	33	↑
Menon, 2006 (57)	Chronic kidney disease	820	323	↑
George, 2006 (69)	Chronic heart failure	175	36	↑
Wannamethee, 2007 (70)	General population	3,099	465	↑
	CVD¶	830	217	↔
	Chronic heart failure¶	117	52	↔
Laughlin, 2007 (71)¶	Community dwelling	1,361	925	↑
Tsutamoto, 2007 (43)	Chronic heart failure	449	47	↑ ↔ç
Dekker, 2008 (72)	General population (with no history of CVD)	1,886	340	↔
	General population (with history of CVD)	433	164	↑
Jorsal, 2008 (73)	Type 1 diabetes (100% end-stage renal disease)	373	98	↑
Rao, 2008 (74)	End-stage renal disease	182	107	↓
Ohashi, 2008 (75)	Hemodialysis	74	15	↑
Lee, 2009 (76)	Acute myocardial infarction	397	28	↑
Poehls, 2009 (44)	General population	3,075	679	↑
Dieplinger, 2009 (77)	Periphery artery disease	487	114	↑
Drechsler, 2009 (78)	Type 2 diabetes (100% hemodialysis)	1,249	617	↔
Mikkelsen, 2010 (79)	Cardiac surgery	836	40	↑
Kizer, 2011 (80)	Community dwelling	840	176	↔ ↑^
Nagasawa, 2011 (81)	Ischemic stroke	548	39	↔
Forsblom, 2011 (82)	Type 1 diabetes	2,034	173	↑
Duggan, 2011 (83)©	Breast cancer	527	62	↔
Waschki, 2011 (84)	Chronic obstructive pulmonary disease	169	26	↑
Koch, 2011 (85)	Critically ill	170	NR	↑
Wannamethee, 2011 (86)¶	General population	2,879	667	↑
Wilson, 2011 (87)	Acute coronary syndrome	3,931	NR	↔
Kizer, 2012 (88)#	General population	3,272	1,947	↔ ↑*
	CVD	1,030	802	↑
	Chronic heart failure or atrial fibrillation	383	337	↑
Beatty, 2012 (46)	Ischemic heart disease	981	375	↑
Lindberg, 2012 (89)	STEMI	735	99	↑
Abdallah, 2012 (90)	Hemodialysis	133	36	↑
Persson, 2012 (91)	Carotid endoarterectomy	292	52	↑
Singer, 2012 (92)	Type 2 diabetes	609	92	↑
Markaki, 2012 (93)	Hemodialysis and peritoneal dialysis	74	18	↑
Yoon, 2012 (94)¶	General population (smokers)	4,686	438	↔
Alam, 2013 (45)	Kidney transplant	952	122	↑
Park, 2013 (95)	End-stage renal disease	131	22	↔
Lindberg, 2013 (96)	General population	5,624	801	↑
Hascoet, 2013 (97)¶	General population (52% with coronary artery disease)	1,497	193	↑
Spoto, 2013 (98)	Hemodialysis	231	165	↓
Uetani, 2014 (60)§	Community dwelling	2,020	84	↑
Menzaghi, 2014 (50)#	Type 2 diabetes (100% coronary artery disease)	359	81	↑
Szabó, 2014 (99)	Chronic heart failure	111	31	↑

Table 1—Continued

First author, year (ref.)	Study population	Subjects (n)	Deaths (n)	Adiponectin-mortality association
Rhee, 2015 (47)	Hemodialysis	501	50	↑
Choi, 2015 (42)	Community dwelling	1,000	222	↑
Chong, 2015 (100)	Colorectal cancer	621	269	↑
Tung, 2015 (101)	Peritoneal dialysis	79	NR	↓
Lindberg, 2015 (102)©	STEMI	720	137	↑
Delgado, 2016 (103)	General population (smokers)	777	221	↑
	General population (nonsmokers)	1,178	302	↑
Witberg, 2016 (104)	General population	3,263	184	↑
Pratesi, 2016 (105)	Coronary artery disease	138	26	↑
Ortega Moreno, 2016 (49)	Type 2 diabetes	1,426	433	↑
Liu, 2016 (59)¶§	Type 2 diabetes	950	580	↑
Zhou, 2016 (106)	Hemodialysis	105	34	↓
Bergmark, 2017 (48)	Type 2 diabetes	5,213	523	↑
Gulin, 2017 (107)	Nontraumatic hip fracture	236	67	↑
Karampela, 2017 (108)#	Intensive care unit	102	30	↔
Ritsinger, 2017 (109)	Acute myocardial infarction	180	61	↔

NR, not reported; STEMI, ST-segment elevation myocardial infarction. ↑, ↔, and ↓, positive, neutral, and inverse correlation, respectively, between adiponectin (i.e., total when not otherwise specified) in fully adjusted models. ¶Only male. ©Only female. §HMW adiponectin. #Total and HMW adiponectin. çPositive or neutral association with total and HMW, respectively. ^Neutral or positive association among individuals with adiponectin < or ≥20 mg/L, respectively. *Neutral or positive association among individuals with adiponectin < or ≥12.4 mg/L, respectively.

insulin (31), a proxy of insulin resistance, thus questioning a direct beneficial role of adiponectin on insulin sensitivity.

Prospective studies are available on the relationship between circulating adiponectin levels and incident type 2 diabetes, the most relevant outcome of insulin resistance. Although meta-analyses of these reports clearly indicate that high adiponectin levels do predict a reduced risk of type 2 diabetes (31,32), a large Mendelian randomization study carried out by using an *ADIPOQ* genetic risk score in more than 80,000 individuals casts doubts about the possibility that this association is sustained by a cause–effect relationship (31).

Although the Mendelian randomization approach has several intrinsic limitations, the extremely high study statistical power that guaranteed the detection of trivial changes of adiponectin variance (31) makes the risk of false-negative results on both insulin sensitivity and type 2 diabetes very unlikely.

In all, while there are strong epidemiological evidences on the associations between low adiponectin levels and both insulin resistance (21,30) and type 2 diabetes (31,32), robust genetic data suggest that they are not sustained by a cause–effect relationship (31). This unexpectedly indicates adiponectin as a simple marker, rather than a real pathogenic factor of these metabolic abnormalities.

Although prospective studies first suggested that adiponectin is a protective molecule for myocardial infarction (33) and coronary artery disease (34), further larger studies and meta-analyses have clearly indicated that low serum adiponectin concentrations do not predict future cardiovascular events (35–38). In a Mendelian randomization study carried out in more than 250,000 individuals, adiponectin-increasing alleles were not associated with reduced risk of coronary heart disease (39), thus reinforcing the idea that adiponectin does not play a role in shaping cardiovascular risk. This again is an unexpected finding, given the favorable effects of adiponectin on lipid metabolism, chronic low-grade inflammation, endothelial function, and several aspects of atherosclerotic processes reported by studies in cellular and animal models (3,7–13,15,18–20). Also, in this case the large study sample size (39) makes the possibility of a false-negative result unlikely.

PARADOXICAL ASSOCIATION OF ADIPONECTIN ON MORTALITY RATE

Circulating adiponectin, both total and HMW adiponectin, has been reported to be positively associated with mortality rate across several clinical sets in the vast majority of available investigations, with only very few and small studies reporting the expected inverse relationship (Tables 1 and 2).

The first of such counterintuitive findings has been reported in patients with ischemic stroke and chronic heart failure (Tables 1 and 2). Similar independent associations have been later reported in asymptomatic elderly participants from the general population and in patients affected by several diseases, including coronary artery disease, peripheral arterial diseases, chronic kidney disease, and cancer. Similarly there are data obtained in patients with type

Table 2—Studies on the association between circulating adiponectin levels and cardiovascular mortality

First author, year (ref.)	Study population	Subjects (n)	Deaths (n)	Adiponectin-mortality association
Pilz, 2006 (67)	General population (78.6% with coronary artery disease)	3,146	427	↑
Cavusoglu, 2006 (68)	General population	325	20	↑
Menon, 2006 (57)	Chronic kidney disease	820	122	↑
Wannamethee, 2007 (70)¶	General population¶	3,099	166	↑
	CVD	830	113	↔
	Chronic heart failure	117	30	↔
Laughlin, 2007 (71)	Community dwelling	1,361	441	↑
Dekker, 2008 (72)	General population (no history of CVD)	1,839	115	↔
	General population (history of CVD)	417	88	↔
Maiolino, 2008 (110)	CVD	712	45	↔
Lee, 2009 (76)	Acute myocardial infarction	397	20	↔
Poehls, 2009 (44)	General population	3,075	247	↑
Dieplinger, 2009 (77)	Periphery artery disease	487	69	↑
Forsblom, 2011 (82)	Type 1 diabetes	2,034	173	↑
Nagasawa, 2011 (81)	Ischemic stroke	548	15	↑
Wannamethee, 2011 (86)	General population	2,879	225	↑
Kizer, 2012 (88)#	General population	3,272	634	↔ ↑*
	CVD	1,030	375	↑
	Chronic heart failure or atrial fibrillation	383	180	↑
Lindberg, 2012 (89)	STEMI	735	50	↑
Yoon, 2012 (94)¶	General population (smokers)	4,686	106	↓
Persson, 2012 (91)	Carotid endoarterectomy	292	27	↑
Spoto, 2013 (98)	Hemodialysis	231	96	↓
Gardener, 2013 (111)	General population	2,091	410	↑
Hascoet, 2013 (97)¶	General population (52% with coronary artery disease)	1,497	117	↑
Menzaghi, 2014 (50)#	Type 2 diabetes (100% with coronary artery disease)	359	58	↑
	Type 2 diabetes©	902	144	↔
	Type 2 diabetes¶	833	146	↑
Choi, 2015 (42)	Community dwelling	1,000	52	↑
Witberg, 2016 (104)	General population	3,263	63	↑
Liu, 2016 (59)§¶$	Type 2 diabetes	950	220	↑
Bergmark, 2017 (48)	Type 2 diabetes	5,213	184	↑
Ritsinger, 2017 (109)	Acute myocardial infarction	180	35	↔

STEMI, ST-segment elevation myocardial infarction. ↑, ↔, and ↓, positive, neutral, and inverse correlation, respectively, between adiponectin (i.e., total when not otherwise specified) in fully adjusted models. ¶Only male. ©Only female. §HMW adiponectin. #Total and HMW adiponectin levels were measured, giving the same results. *No or positive association among individuals with adiponectin < or ≥12.4 mg/L, respectively. $Most of the patients comprised in this study had been already investigated in Menzaghi et al. (50).

1 and type 2 diabetes in whom high adiponectin acts as an independent predictor of both all-cause and cardiovascular mortality.

Although, a meta-analysis of earlier studies (36) suggested that the paradoxical association between increased adiponectin and elevated mortality rate was only observed in the presence of cardiovascular disease (CVD), subsequent studies have clearly indicated that, no matter if total or HMW adiponectin was measured, it does occur across all clinical settings (Tables 1 and 2).

Despite in all prospective studies considered here, the paradoxical relationship between adiponectin and mortality

risk was independent by several covariates (Tables 1 and 2); the intrinsic nature of study design cannot rule out if some factors that are strongly related to both adiponectin and mortality rate have nonetheless confounded it. Among these are several ongoing medications, especially in frail and elderly people, such as those with diabetes and CVD, who are often overtreated.

Given the established role of adiposity on both serum adiponectin levels (40) and mortality (41), BMI also is a candidate confounder/modifier on the counterintuitive association between adiponectin and mortality rate. Unfortunately, studies addressing this subject have shown

discordant results (42–49). In fact, although some studies have reported a preferential adiponectin effect on mortality rate in specific BMI subgroups varying across studies (42–44), others have described no such effect modification in several clinical sets (45–47), including patients with type 2 diabetes (48,49).

We have recently reported that adiponectin levels seem to predict cardiovascular mortality in a sex-specific manner, with the paradoxical effect being observed in men but not women (50). A similar sexual dimorphism has been described also for the associations between adiponectin and other cardiovascular outcomes, including chronic kidney disease (51) and the progression of carotid intima-media thickness (52), suggesting this may be a phenomenon regarding several cardiovascular effects of adiponectin.

The biology underlying the counterintuitive association between high serum adiponectin concentration and increased mortality rate is not yet known, so only speculations can be offered in this article.

A reasonable possibility is that increasing adiponectin is a failing attempt to protect individuals with great risk of mortality. One of the reasons for such failing may be adiponectin resistance in metabolically active organs including the adipose tissue, skeletal muscle, liver, vasculature, and heart (53).

Another possible and certainly very intriguing explanation is that the adiponectin paradox is driven by the direct and strong correlation between adiponectin itself and natriuretic peptides (NPs), established risk factors of mortality rate (54). This hypothesis is based on studies showing that both atrial NP (ANP) and brain NP (BNP) enhance adiponectin production in human adipocytes (55) and that ANP infusion increases plasma adiponectin levels in humans (55). So, according to this hypothesis, NPs would be the real risk

factors of mortality rate, with adiponectin being only a marker of increased NPs. However, studies in which the association between serum adiponectin and mortality rate was conditioned by NP circulating levels have given conflicting results. In detail, after taking into account NPs, the adiponectin paradox was no longer observed in some reports while remaining totally unaffected in others (Table 3). This makes it impossible to draw firm conclusions about the confounding role of NPs on the association between adiponectin and mortality rate.

Last, it could be hypothesized that reduced kidney function, an important cause of premature death (56), also acts as a confounder of the association between adiponectin and mortality (57). However, epidemiological studies do not support this hypothesis (57), with the paradoxical association between adiponectin and mortality rate being either independent (57) or synergic (49) to that of glomerular filtration rate.

By performing a pilot Mendelian randomization study, we have tried to provide our own contribution to unravel the biology underlying the adiponectin paradox (58). In 356 patients with diabetes and established coronary artery disease from the Gargano Heart Study (GHS) prospective design, a GWAS-derived single nucleotide polymorphism (SNP) in the *ADIPOQ* locus was firmly associated with adiponectin levels, as well as with cardiovascular mortality, thus pointing to a direct deleterious role of adiponectin in shaping the risk of death. Completely in contrast with our data (58), Liu et al. (59) found in 950 individuals from the Health Professionals Follow-Up Study (HPFS) that adiponectin-increasing alleles of 19 SNPs, considered together as a genetic risk score, were not associated with cardiovascular mortality in male patients with type 2 diabetes. Several differences across the two studies could explain the

Table 3—Role of NPs on the paradoxical association between circulating adiponectin levels and all-cause mortality rate

First author, year (ref.)	Subjects (*n*)	Deaths (*n*)	NPs	Adiponectin-mortality association	
				Adjustment for NPs	
				No	Yes
Kistorp, 2005 (66)	195	46	NT-proBNP	↑↑	↔
Pilz, 2006 (67)	3,146	482	NT-proBNP	↑↑	↑↑
George, 2006 (69)	175	36	NT-proBNP	↑↑	↑↑
Tsutamoto, 2007 (43)	449	47	ANP, BNP, NT-proBNP	↑↑	↑
Dieplinger, 2009 (77)	487	114	NT-proBNP	↑↑	↔
Drechsler, 2009 (78)	1,255	617	NT-proBNP	↔	↔
Wannamethee, 2011 (86)*	2,879	667	NT-proBNP	↑↑	↑
Wilson, 2011 (87)	3,931	NR	BNP	↔	↔
Beatty, 2012 (46)	981	375	NT-proBNP	↑↑	↑
Szabó, 2014 (99)	111	31	ProANP	↑↑	↑
Lindberg, 2015 (102)	720	137	ProANP	↑↑	↔
Witberg, 2016 (104)*	3,263	184	NT-proBNP	↑↑	↑↑

NR, not reported; NT-proBNP, N-terminal proBNP. ↑↑Positive association. ↑Attenuated positive association. ↔Neutral association. *In these studies, data on cardiovascular mortality are also available and report results similar to those on all-cause mortality.

divergent results, including those in environmental or genetic background or those in the clinical set. Our sample included only white patients with diabetes and established coronary artery disease recruited in a very small and homogeneous region of Central-Southern Italy, and HPFS comprises patients with diabetes recruited from all over the U.S., with only 50% of them having baseline CVD. Notably, when HPFS patients with baseline CVD were excluded from the analysis, the association between adiponectin and cardiovascular mortality was no longer significant. This allows for the hypothesis that in the absence of baseline CVD the adiponectin paradox on mortality risk is attenuated, thus making difficult addressing whether causality underlies it. Furthermore, in study by Liu et al. (59), an indispensable prerequisite of Mendelian randomization study (i.e., a strong association between the genetic instrumental variable and the trait of interest) was not satisfied, thus making the risk of false-negative results likely due to poor statistical power. Some further support to a true deleterious role of adiponectin in increasing mortality risk has been provided by a study reporting that a GWAS-derived SNP in *CDH13* is associated with both increased HMW adiponectin levels and increased mortality rate (60).

Until larger studies are able to provide more robust data about the possible direct deleterious effect of adiponectin on the risk of death, what could we hypothesize would be the mechanism of such paradox? Recently some deleterious effects of adiponectin on inflammatory processes under specific conditions have been reported. In colonic epithelial cells, adiponectin exerted proinflammatory effects by inducing chemokine production (61); also, adiponectin-deficient mice were protected from chemically induced colitis resembling inflammatory bowel disease, whereas adiponectin infusion restored colon inflammation by inducing local production of proinflammatory cytokines (62). In rheumatoid arthritis, recombinant adiponectin induced synthesis of IL-6 and matrix metalloproteinase inhibitor 1 in human synovial fibroblasts via a p38 mitogen-activated protein kinase pathway (63). Moreover, in cultured chondrocytes from patients with rheumatoid arthritis, adiponectin stimulated the expression of vascular endothelial growth factor, monocyte chemoattractant protein 1, vascular cell adhesion molecule 1, and RANTES (i.e., regulated on activation, normal T cell expressed and secreted), all promoting inflammation (63). Finally, in patients with Crohn disease, adiponectin production was enhanced in hypertrophied mesenteric adipose
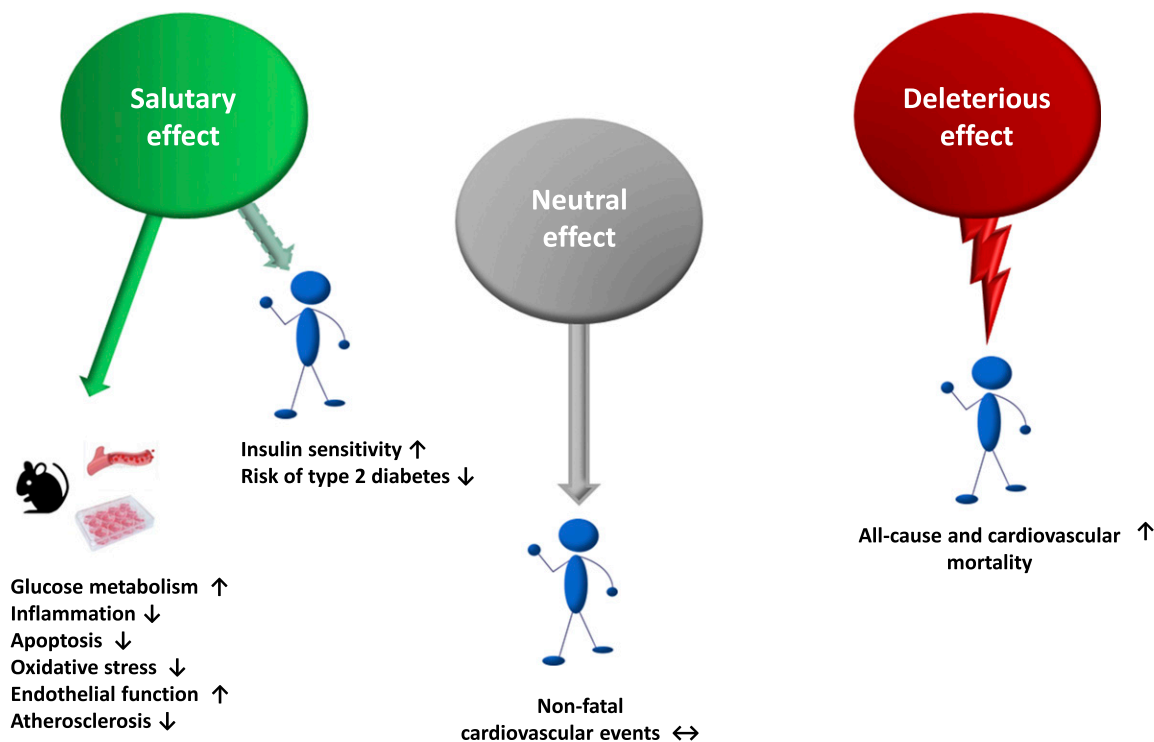

Figure 1—The adiponectin paradox. Quite unexpectedly, given its salutary effects on glucose metabolism, inflammation, and several atherosclerotic processes reported by basic science studies, adiponectin seems to be a mere marker of reduced insulin resistance and type 2 diabetes, with no pathogenic role on these metabolic abnormalities (as stressed by the dashed arrow). Even more unexpected are reports showing that adiponectin exerts a neutral effect on nonfatal cardiovascular events and, paradoxically, a deleterious role on both all-cause and cardiovascular mortality.

tissue as compared with control uninflamed tissue (64). Altogether, these data indicate that under some chronic inflammatory conditions, adiponectin, rather than being an anti-inflammatory factor, exacerbates inflammation in several tissues and cell types. Whether such unexpected deleterious roles of adiponectin on inflammation are also operating during low-grade chronic inflammation characterizing CVD and, in general, many frail individuals at high mortality risk and whether this may explain the adiponectin paradox on mortality rate is a possibility that deserves specifically designed studies to be properly addressed.

CONCLUSIONS

The paradigm of a favorable role of adiponectin on metabolic, inflammation, and atherosclerosis processes (3) has been mostly obtained by pioneering studies carried out in cellular and animal models (3,13,18–20) in which the main findings were compatible with results from early small studies in humans (21–23,27,28). However, when looking at large epidemiological and genetic studies it becomes evident, though totally unexpected, that high serum adiponectin is likely to be a mere marker of insulin sensitivity and glucose homeostasis (31), to be neutral in terms of cardiovascular risk (39), and to paradoxically predict increased all-cause and cardiovascular mortality rate (Tables 1 and 2 and Fig. 1).

Several efforts are definitively needed to better understand the adiponectin paradox on the risk of mortality. Among these is setting up a large collaborative prospective study comprising genetic data to answer the question of whether or not adiponectin does exert a direct deleterious role on the risk of death. The same study will offer the opportunity to deeply investigate the role of NPs (55) and possible sexual dimorphism (50) as confounders or modulators of the adiponectin paradox. Such a study will also make it possible to investigate whether adding circulating adiponectin levels on top of established risk factors improves our ability to predict the risk of mortality across several clinical conditions.

Both basic science and in vivo physiological studies are also needed to understand whether adiponectin resistance underlies the adiponectin paradox and, if so, the intimate molecular mechanism(s) through which this phenomenon occurs.

Finally, only coordinated investigations in cell cultures, animal models, and human beings will address the existence of and mechanisms of adiponectin proinflammatory effects during chronic low-grade inflammation conditions, including CVD, type 2 diabetes, and frailty in elderly people at high mortality risk, and help further the understanding of whether this unexpected scenario plays a role on the adiponectin paradox.

In conclusion, 30 years after its discovery, adiponectin still remains a very elusive molecule. In fact, several epidemiological data question the anti-inflammatory and cardioprotective effects of adiponectin described in basic studies and disappointingly cast doubts on adiponectin as a promising therapeutic target. When it comes to complexity, it does not make sense to try minimizing it: much has been done on adiponectin, but more has to be done.

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