The Cardioprotective Effects of Adiponectin in Diabetes

Tara Kazemi[1], Yuanjie Mao, M.D., Ph.D.[1,2,3], Tina Zhang[4]

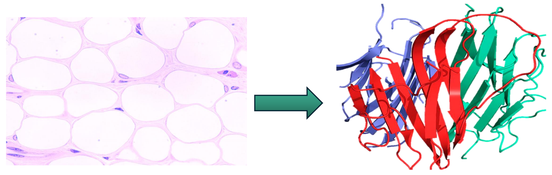
1. Ohio University Heritage College of Osteopathic Medicine, Athens, OH 45701, USA
2. Diabetes Institute, Ohio University, Athens, Ohio 45701, USA.
3. Endocrinology & Diabetes Clinic, OhioHealth Castrop Health Center, Athens, Ohio 45701, USA.
4. Department of Biological Sciences, University of Pittsburgh, Pittsburgh, PA, 15213, USA.

Abstract

- **Adiponectin**, a hormone secreted by adipocytes, supports **metabolic balance** and **cardiovascular health** through anti-inflammatory and insulin-sensitizing effects.
- Yet in **T1D**, **T2D**, and **heart failure**, **high adiponectin levels paradoxically correlate with worse outcomes** a phenomenon known as the **adiponectin paradox**.
- This review synthesizes findings on adiponectin's dual roles, focusing on its signaling mechanisms, disease-specific patterns, and implications for **personalized risk stratification and therapy.**

Introduction

- **Adiponectin** improves **glucose metabolism**, **insulin sensitivity**, and **vascular function**, and is typically considered protective[1-3].
- However, in advanced **diabetes** and **heart failure**, elevated levels are associated with **adiponectin resistance** and **worse clinical outcomes** — the **adiponectin paradox**[4,5].
- Given the rising burden of cardiovascular complications in both **T1D** and **T2D**, understanding how adiponectin signaling shifts from protective to maladaptive is critical for guiding **targeted interventions**.



White Adipocytes

Adiponectin Hormone

Methodology

- Literature search conducted in PubMed and Embase (2000–2025) for studies examining **adiponectin in T1D, T2D, and heart failure**.
- Focused on studies reporting serum levels, receptor signaling, and cardiovascular outcomes.
- Included clinical, translational, and mechanistic studies; excluded non-English and non-diabetes-related reports.
- Data were synthesized to highlight protective functions, paradoxical associations, and disease-specific dynamics.

Results

Adiponectin: From Protection to Paradox

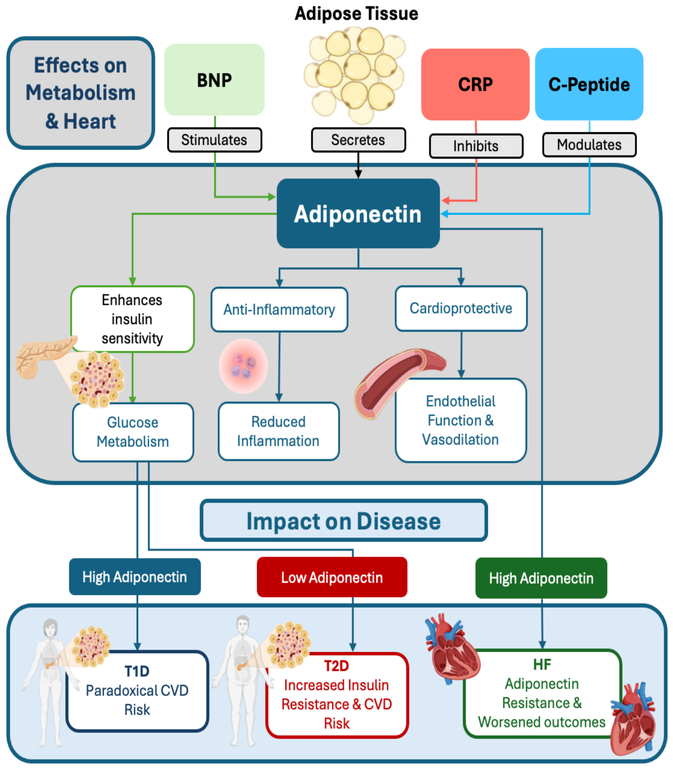
Protective Functions

- Activates **AMPK** and **PPAR-α**, → ↑ glucose uptake & fat oxidation[6,7]
- Enhances **GLUT4** in muscle → ↑ insulin sensitivity[8]
- Suppresses **NF-κB** → ↓ inflammation[6]
- Promotes **eNOS** activity → improved vascular dilation[15]
- Example: Adiponectin therapy improved LVEF by **15%** and reduced fibrosis by **25%** post-MI[16]

The Adiponectin Paradox:

High levels **predict protection in health**, but in **T1D, T2D, and HF** are linked to **worse outcomes**[2,5,12].

- Why? Likely due to a**diponectin resistance**:
  - ↓ AdipoR1 expression by **40%** in T2D muscle → impaired AMPK activation[9]
  - Oxidative/inflammatory stress disrupts receptor binding[3,11]
  - BNP-driven secretion in HF increases circulating levels but not function[59-61]



Feature	T1D	T2D	HF
C-Peptide	Low/absent (β-cell destruction)[17]	Normal or high early, ↓ later[1]	Variable; may be normal or low
Adiponectin	High early (28–98% ↑ vs controls)[13,14]	Low early (30–50% ↓)[1], paradoxical ↑ in late stage[12]	Very high, ↑ with BNP[20-23]
C-Reactive Protein (CRP)	Mild elevation later in disease[5]	High early due to inflammation[11]	Elevated, tracks with systemic inflammation[15,12]
Risk Pattern	Paradoxical ↑ CV risk despite high levels[2]	Biphasic: low = resistance, high = paradoxical ↑ CV risk[12]	High adiponectin = ↑ mortality (HR = 1.67)[17]
Mechanism	Insulin deficiency → resistance[28]	Visceral fat + inflammatory cytokine suppression[10,11]	BNP-stimulated but ineffective[58-61]

Adiponectin Levels Vary by Disease Type

Elevated Adiponectin in Type 1 Diabetes (T1D)

- Serum levels ↑ by **28–98%** vs controls[13,14] Caused by **insulin deficiency** and **low C-peptide**.
  → Normally, insulin *inhibits* adiponectin secretion. Without it, levels ↑
- Inverse with BMI; positive with HDL[13]
- High adiponectin → **40% ↑ cardiovascular event risk**[2]
- Evidence of **tissue resistance** despite high levels[15]

Decreased Adiponectin in Type 2 Diabetes (T2D)

- Serum adiponectin ↓ by **30–50%** vs healthy individuals[1]
- Strong inverse correlation with visceral fat ($r = -0.57$, $P<0.001$)[10]
- Inflammatory cytokines (TNF-α, IL-6) ↓ secretion by **20–30%**[11]
- Late-stage rise = marker of **advanced metabolic stress**, not protection[12]

Heart Failure (HF)

- BNP drives **adiponectin secretion** during stress[20-23]
- Levels ↑ with HF severity[12]
- Highest quartile adiponectin levels → **67% ↑ mortality risk** (HR = 1.67, 95% CI: 1.24–2.26)[16]
- Post-VAD therapy: adiponectin fell **13.3 → 7.4 μg/mL**, improving insulin sensitivity[19]

Conclusion

Adiponectin plays a vital regulatory role in both metabolic and cardiovascular health, influencing:

- Insulin sensitivity
- Lipid metabolism
- Inflammatory signaling
- Oxidative stress response

While protective under normal conditions, the situation where high adiponectin levels do not translate into beneficial insulin sensitivity and health benefits seen in T1D, T2D, and HF is often referred to as **"the adiponectin paradox"** [12].

Disease-Specific Dynamics

- **T1D**: High adiponectin early (from insulin deficiency), but becomes ineffective as resistance develops
- **T2D**: Low adiponectin early (due to visceral fat/inflammation); late-stage increases signal metabolic failure
- **Heart Failure**: BNP-driven rise in adiponectin fails to deliver benefit due to systemic and cardiac resistance

Implications & Future Directions

- Recognizing adiponectin resistance, not just levels, is key to interpretation
- Therapies targeting **AdipoR1/R2** and downstream signaling (e.g., AMPK activation) may restore function
- **Combined biomarkers** (e.g., adiponectin + BNP) could enhance risk stratification in diabetes and HF
- Further research is needed to define mechanisms and tailor treatments based on disease stage and context

References

1. Khoramipour, K., Chamari, K., Hekmatikar, A. A., Ziyaiyan, A., Taherkhani, S., Elguindy, N. M., & Bragazzi, N. L. (2021). Adiponectin: Structure, physiological functions, role in diseases, and effects of nutrition. In *Nutrients* (Vol. 13, Issue 4). MDPI AG. https://doi.org/10.3390/nu13041180
2. Mao, Y., & Zhong, W. (2023). Serum adiponectin concentrations as a risk factor for cardiovascular complications in type 1 diabetes. *Diabetes Research and Clinical Practice*, *200*. https://doi.org/10.1016/j.diabres.2023.110700
3. Wang, Y., Ma, X. L., & Lau, W. B. (2017). Cardiovascular Adiponectin Resistance: The Critical Role of Adiponectin Receptor Modification. In *Trends in Endocrinology and Metabolism* (Vol. 28, Issue 7, pp. 519–530). Elsevier Inc. https://doi.org/10.1016/j.tem.2017.03.004
4. Arita, Y., Kihara, S., Ouchi, N., Takahashi, M., Maeda, K., Miyagawa, J. I., Hotta, K., Shimomura, I., Nakamura, T., Miyaoka, K., Kuriyama, H., Nishida, M., Yamashita, S., Okubo, K., Matsubara, K., Muraguchi, M., Ohmoto, Y., Funahashi, T., & Matsuzawa, Y. (1999). Paradoxical Decrease of an Adipose-Specific Protein, Adiponectin, in Obesity. *Biochemical and Biophysical Research Communications*, *257*(1), 79–83. https://doi.org/10.1006/BBRC.1999.0255
5. Forsblom, C., Thomas, M. C., Moran, J., Saraheimo, M., Thorn, L., Wadén, J., Gordin, D., Frystyk, J., Flyvbjerg, A., & Groop, P. H. (2011). Serum adiponectin concentration is a positive predictor of all-cause and cardiovascular adip in type 1 diabetes. *Journal of Internal Medicine*, *270*(4), 346–355. https://doi.org/10.1111/j.1365-2796.2011.02406.x
6. Han, Y., Sun, Q., Chen, W., Gao, Y., Ye, J., Chen, Y., Wang, T., Gao, L., Liu, Y., & Yang, Y. (2024). New advances of adiponectin in regulating obesity and related metabolic syndromes. In *Journal of Pharmaceutical Analysis* (Vol. 14, Issue 9). https://doi.org/10.1016/j.jpha.2023.12.003
7. Kadowaki, T., Yamauchi, T., Kubota, N., Hara, K., Ueki, K., & Tobe, K. (2006). Adiponectin and adiponectin receptors in insulin resistance, diabetes, and the metabolic syndrome. In *Journal of Clinical Investigation* (Vol. 116, Issue 7, pp. 1784–1792). https://doi.org/10.1172/JCI29126
8. Yamauchi, T., Kamon, J., Minokoshi, Y., Ito, Y., Waki, H., Uchida, S., Yamashita, S., Noda, M., Kita, S., Ueki, K., Eto, K., Akanuma, Y., Froguel, P., Foufelle, F., Ferre, P., Carling, D., Kimura, S., Nagai, R., Kahn, B. B., & Kadowaki, T. (2002). Adiponectin stimulates glucose utilization and fatty-acid oxidation by activating AMP-activated protein kinase. *Nature Medicine*, *8*(11), 1288–1295. https://doi.org/10.1038/nm788
9. Sharma, A., Mah, M., Ritchie, R. H., & de Blasio, M. J. (2022). The adiponectin signaling pathway - A therapeutic target for the cardiac complications of type 2 diabetes? In *Pharmacology and Therapeutics* (Vol. 232). Elsevier Inc. https://doi.org/10.1016/j.pharmthera.2021.108009
10. Ljubic, S., Boras, J., Jazbec, A., Phd, B., Lovrencic, M. V., Vidjak, V., Jurisic Erzen, D., & Mileta, D. (2009). *Adiponectin has different mechanisms in type 1 and type 2 diabetes with C-peptide link.*
11. Kern, P. A., Ranganathan, S., Wood, L., Ranganathan, G., Li, C., & Ranganathan Adipose, G. (2001). Adipose tissue tumor necrosis factor and interleukin-6 expression in human obesity and insulin resistance. In *Am J Physiol Endocrinol Metab* (Vol. 280). http://www.ajpendo.orgE745
12. Menzaghi, C., & Trischitta, V. (2018). The adiponectin paradox for all-cause and cardiovascular mortality. *Diabetes*, *67*(1), 12–22. https://doi.org/10.2337/dbi17-0016
13. Maahs, D. M., Ogden, L. G., Snell-Bergeon, J. K., Kinney, G. L., Wadwa, R. P., Hokanson, J. E., Dabelea, D., Kretowski, A., Eckel, R. H., & Rewers, M. (2007). Determinants of serum adiponectin in persons with and without type 1 diabetes. *American Journal of Epidemiology*, *166*(8), 731–740. https://doi.org/10.1093/aje/kwm125
14. Frystyk, J., Tarnow, L., Krarup Hansen, T., Parving, H. H., & Flyvbjerg, A. (2005). Increased serum adiponectin levels in type 1 diabetic patients with microvascular complications. *Diabetologia*, *48*(9), 1911–1918. https://doi.org/10.1007/s00125-005-1850-z
15. Farah, C., Michel, L. A Ballgand, JL Nitric oxide signalling in cardiovascular health and disease. *Nat Rev Cardiol* 15, 292–316 (2018). https://doi.org/10.1038/nrcardio.2017.224E
16. Zhou, Z., Liu, C., Xu, S. *et al.* Metabolism regulator adiponectin prevents cardiac remodeling and ventricular arrhythmias via sympathetic modulation in a myocardial infarction model. *Basic Res Cardiol* 117, 34 (2022). https://doi.org/10.1007/s00395-022-00939-2
17. Beatty, A. L., Zhang, M. H., Ku, I. A., Na, B., Schiller, N. B., & Whooley, M. A. (2012). Adiponectin is associated with increased mortality and heart failure in patients with stable ischemic heart disease: Data from the Heart and Soul Study. *Atherosclerosis*, *220*(2), 587–590. https://doi.org/10.1016/j.atherosclerosis.2011.11.038
18. Jang, A. Y., Scherer, P. E., Kim, J. Y., Lim, S., & Koh, K. K. (2022). Adiponectin and cardiometabolic trait and mortality: where do we go? In *Cardiovascular Research* (Vol. 118, Issue 9, pp. 2074–2084). Oxford University Press. https://doi.org/10.1093/cvr/cvab199
19. Khan, R. S., Kato, T. S., Chokshi, A., Chew, M., Yu, S., Wu, C., Singh, P., Cheema, F. H., Takayama, H., Harris, C., Reyes-Soffer, G., Knöll, R., Miting, H., Naka, Y., Mancini, D., & Schulze, P. C. (2012). Adipose tissue inflammation and adiponectin resistance in patients with advanced heart failure:correction after ventricular assist device implantation. *Circulation: Heart Failure*, *5*(3), 340–348. https://doi.org/10.1161/CIRCHEARTFAILURE.111.964221
20. Takano, H., Obata, J. ei, Kodama, Y., Kitta, Y., Nakamura, T., Mende, A., Kawabata, K. ichi, Saito, Y., Fujioka, D., Kobayashi, T., Yano, T., Sano, K., & Kugiyama, K. (2009). Adiponectin is released from the heart in patients with heart failure. *International Journal of Cardiology*, *132*(2), 221–226. https://doi.org/10.1016/j.ijcard.2007.11.040
21. Tamura T, Furukawa Y, Taniguchi R, Sato Y, Ono K, Horiuchi H, Nakagawa Y, Kita T, Kimura T. Serum adiponectin level as an independent predictor of mortality in patients with congestive heart failure. Circ J. 2007 May;71(5):623-30. doi: 10.1253/circj.71.623. PMID: 17456962.
22. Tsukamoto, O., Fujita, M., Kato, M., Yamazaki, S., Asano, Y., Ogai, A., Okazaki, H., Asai, M., Nagamachi, Y., Maeda, N., Shintani, Y., Minamino, T., Asakura, M., Kishimoto, I., Funahashi, T., Tomoike, H., & Kitakaze, M. (2009). Natriuretic Peptides Enhance the Production of Adiponectin in Human Adipocytes and in Patients With Chronic Heart Failure. *Journal of the American College of Cardiology*, *53*(22), 2070–2077. https://doi.org/10.1016/j.jacc.2009.02.033
23. Baldassarroi S, Antenore A, Di Serio C, Orso F, Lonetto G, Bartoli N, Foschini A, Marella A, Pratesi A, Scarantino S, Funagalli S, Monami M, Mannucci E, Marchionni N, Tarantini F. Adiponectin, diabetes and ischemic heart failure: a challenging relationship. Cardiovasc Diabetol. 2012 Dec 18;11:151. doi: 10.1186/1475-2840-11-151. PMID: 23249664; PMCID: PMC3558365.