Senotherapeutic Effects of AdipoAI Unveiling a Novel Treatment for Diabetic Bone Disease

Qisheng Tu, Rebecca Johnson, Akash Ahuja, Xingwen Wu, Jake Chen
Tufts University School of Dental Medicine, Boston, MA, United States
Qisheng.tu@tufts.edu

Disclosures: Qisheng. Tu (N), Rebecca Johnson (N), akash ahuja (N), Xingwen Wu (N), Jake Chen (N)

INTRODUCTION: There is evidence that suggests a link between type 2 diabetes (T2D) and an increased risk of bone-related issues, including osteoporosis. Osteoporosis is characterized by diminished bone density and an elevated fracture risk. Central to T2D-related complications are chronic inflammation and cellular senescence, processes in which senescent cells release pro-inflammatory factors, exacerbating tissue damage and inflammation.

Adiponectin, an antidiabetic adipokine, plays a protective role in metabolic disturbances associated with obesity. Agonists of adiponectin receptor (AdipoR) not only inhibit inflammation and mitigate diabetes but also enhance overall survival and promote healthy aging in animal models. AdipoAI, a newly designed and synthesized analogue of endogenous adiponectin receptor in our lab, demonstrated significantly stronger pharmacological effects than the other adiponectin receptor agonists. Whether AdipoAI could inhibit cellular senescence and exert a senotherapeutic effect on diabetic mice needs further research. In this study, we aim to investigate the impact of AdipoAI on inflammation and senescence under the condition of T2D in an animal model.

METHODS: Using a high-fat diet-induced obesity (DIO) mouse model, we examined the effects of AdipoAI on inflammation and senescence. Additionally, we treated osteoblasts, C2C12 myotubes, and pancreatic beta cells with AdipoAI to assess its direct effects on these cell types. Statistical analysis was performed using one-way ANOVA with multiple comparison between groups, the values of $p<0.05$ were considered as statistically significant.

RESULTS: In vitro treatment with AdipoAI led to an increase in adiponectin receptor subunits AdipoR1/R2, elevated AMPK and APPL1 protein expression in C2C12 myotubes. It concurrently reduced the expression of senescence markers (P16 and P21) and inhibited pro-inflammatory cytokines and senescence-associated secretory phenotype (SASP) markers (IL-1β, TGF-β1 and PAI1/SERPINE1) in osteoblasts and liver tissues under diabetic conditions. Furthermore, AdipoAI stimulated insulin secretion in beta cells. In DIO mice, AdipoAI treatment significantly enhanced blood glucose control, improved insulin sensitivity, and ameliorated bone microarchitecture.

DISCUSSION:

1. AdipoAI and Cellular Signaling: The observed increase in adiponectin receptor subunits (AdipoR1/R2) and elevated AMPK and APPL1 protein expression in C2C12 myotubes following AdipoAI treatment suggests a potential role in enhancing cellular signaling pathways. Adiponectin, a key adipokine, is known for its insulin-sensitizing and anti-inflammatory properties. The upregulation of its receptors and associated proteins in muscle cells by AdipoAI implies a positive modulation of insulin signaling and metabolic homeostasis.
2. Senescence and Inflammation Modulation: Notably, AdipoAI demonstrated a dual effect by reducing the expression of senescence markers (P16 and P21) and inhibiting pro-inflammatory cytokines and SASP markers (IL-1β, TGF-β1, and PAI1/SERPINE1) in osteoblasts and liver tissues under diabetic conditions. This anti-senescence and anti-inflammatory profile suggests a potential therapeutic avenue for managing complications associated with diabetes, such as impaired bone health and liver dysfunction.
3. Insulin Secretion and Beta Cell Function: The observed stimulation of insulin secretion in beta cells by AdipoAI further supports its potential as a regulator of pancreatic function. Improved insulin secretion is crucial in maintaining glucose homeostasis, and the findings suggest that AdipoAI may contribute to enhanced beta cell activity, which is particularly significant in the context of diabetes management.
4. *In Vivo* Effects in DIO Mice: In DIO mice, AdipoAI treatment demonstrated significant improvements in blood glucose control, insulin sensitivity, and bone microarchitecture. These findings suggest that AdipoAI may have systemic effects on metabolic parameters, addressing not only glucose regulation but also potential implications on bone health in the context of obesity-induced complications.
5. Implications for Therapeutic Development: The collective outcomes of this study underscore the multifaceted potential of AdipoAI as a therapeutic agent. Its ability to modulate cellular signaling, mitigate senescence and inflammation, stimulate insulin secretion, and improve metabolic parameters *in vivo* positions AdipoAI as a promising candidate for further exploration in the development of novel treatments for diabetes and associated complications.

In conclusion, the results presented in this study provide valuable insights into the diverse effects of AdipoAI at the cellular and organismal levels. Our groundbreaking study provides the first evidence of AdipoAI's potential in treating T2D and its association with bone disease through senolytic and senomorphic effects, notably via modulating the TGF-β signaling pathway. The observed positive outcomes across various parameters warrant further investigations to elucidate the underlying molecular mechanisms and to determine the translational potential of AdipoAI for clinical applications in the management of diabetes and related disorders.

SIGNIFICANCE/CLINICAL RELEVANCE: AdipoAI emerges as a promising therapeutic agent for addressing T2D-related complications, including osteoporosis and other age-related diseases. The clinical relevance of this study lies in the potential of AdipoAI to serve as a versatile therapeutic agent addressing various facets of metabolic health. Further clinical trials and mechanistic studies will be crucial to fully elucidate the translational impact and safety profile of AdipoAI in human subjects.

ACKNOWLEDGEMENTS: NIH funded this study via grants DK131444 and DE26507 to JC.