DOI: 10.1111/jch.13453

COMMENTARY

WILEY

Diabetes, body fat, skeletal muscle, and hypertension: The ominous chiasmus?

Jun Shu MD[1] | Alessandro Matarese MD[2] | Gaetano Santulli MD, PhD[1,3]

[1]Department of Medicine, Albert Einstein College of Medicine, Montefiore University Hospital, New York, New York

[2]Department of Pneumology and Oncology, AORN "Ospedale dei Colli", Naples, Italy

[3]Department of Biomedical Advanced Sciences, "Federico II" University, Naples, Italy

Correspondence
Gaetano Santulli, Department of Medicine, Albert Einstein College of Medicine, Montefiore University Hospital, New York, NY.
Email: gsantulli001@gmail.com

Funding information
NIH, Grant/Award Number: DK107895

1 | HYPERTENSION AND BODY FAT: AN INTRICATE RELATIONSHIP

In addition to genetic and environmental factors known to play a role in the development of hypertension, body weight and obesity are highly correlated with hypertension; indeed, there is robust evidence that the prevalence of hypertension increases sharply with increasing body weight.[1-4] Importantly, obesity has been shown to shift the secretory profile of the adipose tissue, which in turn contributes to the dysregulation of blood pressure; these phenomena occur through both direct actions of circulating adipokines on the vasculature and indirect actions via other systems, including the renal, central, and peripheral nervous system. For instance, leptin, which is elevated in obesity, increases blood pressure through activation of central nervous system pathways and enhancing the sympathetic nervous system output. Increased expression of pro-inflammatory adipokines in obesity, such as tumor necrosis factor-α (TNF-α), promotes vascular dysfunction through alterations in endothelial function and thickening of the vascular smooth muscle layer. These events, in turn, lead to increased oxidative stress and stiffening of the vascular wall, promoting changes in vessel reactivity. Other adipokines that have been shown to increase blood pressure include chemerin, which increases oxidative stress and impairs vasodilation, and visfatin, which stimulates proliferation of smooth muscle cells.[1]

In a British study performed in 50 436 individuals, Han and collaborators have demonstrated that, compared with normotensive individuals, body fat is significantly higher and skeletal muscle mass significantly lower in any sub-category of hypertension: undetected, adequately controlled, inadequately controlled, and untreated hypertension, both in men and women.[5] Therefore, estimates of both body fat and skeletal muscle mass should be considered when analyzing results from health surveys (also using validated anthropometric prediction equations[6,7] when actual measurements are not possible), rather than relying on body mass index (BMI), which does not discriminate between these two fundamental parameters.

2 | DIABETES AND SKELETAL MUSCLE: WHAT IS KNOWN?

Musculoskeletal disorders have been observed in diabetic patients, and abnormal changes in morphological properties in both slow and fast fibers have been reported as well.[8] Skeletal muscle insulin resistance is considered a core defect in type 2 diabetes, and hyperinsulinemia has been shown to be not only a compensatory response to insulin resistance but also a self- perpetuating cause of the defect in muscle insulin action.[9-11] Additionally, reduced muscle mass may further aggravate metabolic impairment, since the skeletal muscle is the primary site of glucose uptake and deposition. Most recently, diabetes has been associated with reduced mitochondrial function in the skeletal muscle[8] , whereas sarcopenia, defined as loss of lean muscle mass,[12] has been identified as an actual chronic complication of diabetes mellitus.[13] Equally important, a reduced muscular mass has been reported in subjects with metabolic syndrome,[14,15] a cluster of at least three out of five cardiovascular risk factors.[16]

Muscle loss represents a decrease in the mass of insulin-responsive target tissue. This phenomenon promotes insulin resistance, metabolic syndrome, obesity, and hypertension.[17] Seminal

This Commentary refers to JCH-18-0324: "Associations of body fat and skeletal muscle with Hypertension".

clinical studies have shown that the skeletal muscle is a major site of insulin resistance in essential hypertension and that such defect is independent of muscle perfusion[18]; moreover, insulin triggers an abnormal muscle sympathetic activity in essential hypertension.[19]

Notably, exercise training has been proved to be the intervention that most comprehensively improves the diverse aspects of mitochondrial function, along with whole-body and skeletal muscle insulin sensitivity.[8,12,20,21]

3 | HYPERTENSION AND SKELETAL MUSCLE: RECENT EVIDENCE

Blood pressure is directly associated with body size[22]; however, total body mass contains two factors that have opposite biological effects: adipose tissue and lean mass.[5] Subjects with sarcopenia commonly experience functional impairment and physical disability, which may cause a reduction in muscle contraction-induced factors having anti-inflammatory effects, known as myokines[23]: the relative paucity of myokines in sarcopenia may increase the risk of cardiovascular disorders, including hypertension.[24,25] Subjects with sarcopenic obesity have a greater risk of hypertension than simply obese or sarcopenic subjects.[26] Sarcopenic obesity, defined by appendicular muscle mass/body weight, was found to be more closely associated with metabolic syndrome than either obesity or sarcopenia alone.[24,27] Therefore, sarcopenia and obesity might act synergistically on both metabolic and functional impairments. Indeed, a decreased muscle capacity has been observed in the spontaneously hypertensive rat.[28] Moreover, low muscle mass has been recently associated with arterial stiffness and cognitive impairment[29] and also with an increased cardiometabolic risk regardless of nutritional status.[30]

Exercise has been long documented to improve blood pressure, even in obese individuals in absence of weight loss.[31,32] The modulation of the adrenergic system has been shown to be a crucial mechanism underlying the beneficial effects of exercise in hypertensive patients.[31,33-36] Another potential mechanism is the increase in skeletal muscle mass, which has been demonstrated to be modulated by myostatin, a fundamental negative regulator of muscle growth; interestingly, myostatin is upregulated in obesity and downregulated by exercise,[37] and preclinical studies have shown that increased muscle mass can reduce blood pressure in obesity, as well as improve glucose tolerance and renoprotection, independent of changes in body weight and/or adiposity.[38,39]

4 | DIABETES AND BODY FAT: A LONG-STANDING LIAISON

Obesity is the major risk factor for the development of pre-diabetes and type 2 diabetes. The National Health and Nutrition Examination Survey (NHANES) has verified that the BMI is positively associated with the prevalence of metabolic syndrome.[40] Despite being widely used as a surrogate measure of obesity, BMI underestimates the prevalence of obesity, defined as an excess of body fat.[41] Indeed, clinical studies have demonstrated that the actual body fat amount is playing an essential role in the development of insulin resistance and that maintaining normal body fat is significantly more relevant than BMI in preventing diabetes.[41-43] Several epidemiological studies have confirmed that BMI alone may lack predictive value for type 2 diabetes due to differences in muscle mass and fat mass (particularly abnormal adiposity) for the same BMI value.[41,44,45] A significant proportion of people with a normal BMI (18.5-24.9 kg/m^2) has been shown to have pre-diabetes, undiagnosed diabetes, and hypertension.[46,47] Moreover, the increase in body fat has been shown to represent an independent risk factor for new-onset diabetes after transplantation,[48] a serious metabolic complication that can follow organ transplantation.[49,50]

5 | HYPERTENSION AND DIABETES MELLITUS: THE ULTIMATE VICIOUS ASSOCIATION?

Epidemiological and pathological data indicate that diabetes represents an independent risk factor for cardiovascular disease.[51-54] As incident diabetes is more frequent in hypertensive than normotensive subjects,[55] the incidence of hypertension is twofold higher in subjects with diabetes relative to aged-matched individuals without diabetes.[56,57] Moreover, uncontrolled blood pressure is associated with a twofold increased risk of incident diabetes in treated hypertensive patients,[58] and the presence of hypertensive target organ damage increases the risk of diabetes independent of anti-hypertensive treatment and metabolic profile.[59]

Insulin has opposing vasodilator and vasoconstrictor actions (eg, simultaneously stimulating both production of nitric oxide and secretion of endothelin-1) such that the net hemodynamic effect of insulin on blood pressure is minimal in healthy humans; for instance, intravenous insulin infusion significantly increases heart rate and cardiac output and decreases total peripheral resistance.[35,60]

A strong association between hypertension and sarcopenia has been proven in diabetic patients: in a Korean study, the prevalence of hypertension among elderly diabetic adults was 70.3%, and the risk of hypertension was fourfold higher in diabetic patients with obese sarcopenia relative to patients without.[26] Intriguingly, the above-mentioned study by Han and colleagues[5] also revealed that diabetic patients had higher body fat and lower muscle mass, calculated as percentage of body weight, than non-diabetic individuals, for any given hypertensive status, as such opening new fields of investigations in order to determine the exact molecular mechanisms underlying these findings.

ACKNOWLEDGMENT

GS is supported by the NIH (DK107895).

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

ORCID

Gaetano Santulli https://orcid.org/0000-0001-7231-375X

REFERENCES

1. Huang Cao ZF, Stoffel E, Cohen P. Role of perivascular adipose tissue in vascular physiology and pathology. *Hypertension*. 2017;69:770-777.
2. de Simone G, Mancusi C, Izzo R, Losi MA, Ferrara LA. Obesity and hypertensive heart disease: focus on body composition and sex differences. *Diabetol Metab Syndr*. 2016;8:79.
3. Hall JE, do Carmo JM, da Silva AA, Wang Z, Hall ME. Obesity-induced hypertension. *Circ Res*. 2015;116:991-1006.
4. Hall JE. Hyperinsulinemia: a link between obesity and hypertension? *Kidney Int*. 1993;43:1402-1417.
5. Han TS, Al-Gindan YY, Govan L, Hankey CR, Lean MEJ. Associations of body fat and skeletal muscle with hypertension. *J Clin Hypertens*. 2018. https://doi.org/10.1111/jch.13456. [Epub ahead of print]
6. Kulkarni B, Kuper H, Taylor A, et al. Development and validation of anthropometric prediction equations for estimation of lean body mass and appendicular lean soft tissue in Indian men and women. *J Appl Physiol*. 2013;1985(115):1156-1162.
7. Gomez-Ambrosi J, Silva C, Catalan V, et al. Clinical usefulness of a new equation for estimating body fat. *Diabetes Care*. 2012;35:383-388.
8. Hesselink MK, Schrauwen-Hinderling V, Schrauwen P. Skeletal muscle mitochondria as a target to prevent or treat type 2 diabetes mellitus. *Nat Rev Endocrinol*. 2016;12:633-645.
9. DeFronzo RA, Tripathy D. Skeletal muscle insulin resistance is the primary defect in type 2 diabetes. *Diabetes Care*. 2009;32(Suppl 2):S157-S163.
10. Ciccarelli M, Chuprun JK, Rengo G, et al. G protein-coupled receptor kinase 2 activity impairs cardiac glucose uptake and promotes insulin resistance after myocardial ischemia. *Circulation*. 2011;123:1953-1962.
11. Cipolletta E, Del Giudice C, Santulli G, Trimarco B, Iaccarino G. Opposite effects of beta2-adrenoceptor gene deletion on insulin signaling in liver and skeletal muscle. *Nutr Metab Cardiovasc Dis*. 2017;27:615-623.
12. Umanskaya A, Santulli G, Xie W, Andersson DC, Reiken SR, Marks AR. Genetically enhancing mitochondrial antioxidant activity improves muscle function in aging. *Proc Natl Acad Sci USA*. 2014;111:15250-15255.
13. Trierweiler H, Kisielewicz G, Hoffmann Jonasson T, Rasmussen Petterle R, Aguiar Moreira C, Zeghbi Cochenski Borba V. Sarcopenia: a chronic complication of type 2 diabetes mellitus. *Diabetol Metab Syndr*. 2018;10:25.
14. Atlantis E, Martin SA, Haren MT, Taylor AW, Wittert GA. Inverse associations between muscle mass, strength, and the metabolic syndrome. *Metabolism*. 2009;58:1013-1022.
15. Kim K, Park SM. Association of muscle mass and fat mass with insulin resistance and the prevalence of metabolic syndrome in Korean adults: a cross-sectional study. *Sci Rep*. 2018;8:2703.
16. Sardu C, Carreras G, Katsanos S, et al. Metabolic syndrome is associated with a poor outcome in patients affected by outflow tract premature ventricular contractions treated by catheter ablation. *BMC Cardiovasc Disord*. 2014;14:176.
17. Ciccarelli M, Santulli G, Pascale V, Trimarco B, Iaccarino G. Adrenergic receptors and metabolism: role in development of cardiovascular disease. *Front Physiol*. 2013;4:265.
18. Capaldo B, Lembo G, Napoli R, et al. Skeletal muscle is a primary site of insulin resistance in essential hypertension. *Metabolism*. 1991;40:1320-1322.
19. Lembo G, Napoli R, Capaldo B, et al. Abnormal sympathetic overactivity evoked by insulin in the skeletal muscle of patients with essential hypertension. *J Clin Invest*. 1992;90:24-29.
20. De Rosa M, Gambardella J, Shu J, Santulli G. Dietary fat is a key determinant in balancing mitochondrial dynamics in heart failure: a novel mechanism underlying the obesity paradox. *Cardiovasc Res*. 2018;114:925-927.
21. Goedecke JH, Micklesfield LK. The effect of exercise on obesity, body fat distribution and risk for type 2 diabetes. *Med Sport Sci*. 2014;60:82-93.
22. Evans JM, Wang S, Greb C, et al. Body size predicts cardiac and vascular resistance effects on men's and women's blood pressure. *Front Physiol*. 2017;8:561.
23. Fiuza-Luces C, Santos-Lozano A, Joyner M, et al. Exercise benefits in cardiovascular disease: beyond attenuation of traditional risk factors. *Nat Rev Cardiol*. 2018;15:731-743.
24. Kalyani RR, Corriere M, Ferrucci L. Age-related and disease-related muscle loss: the effect of diabetes, obesity, and other diseases. *Lancet Diabetes Endocrinol*. 2014;2:819-829.
25. Srikanthan P, Hevener AL, Karlamangla AS. Sarcopenia exacerbates obesity- associated insulin resistance and dysglycemia: findings from the National Health and Nutrition Examination Survey III. *PLoS ONE*. 2010;5:e10805.
26. Han K, Park Y-M, Kwon H-S, et al. Sarcopenia as a determinant of blood pressure in older Koreans: findings from the Korea National Health and Nutrition Examination Surveys (KNHANES) 2008–2010. *PLoS ONE*. 2014;9:e86902.
27. Lim S, Kim JH, Yoon JW, et al. Sarcopenic obesity: prevalence and association with metabolic syndrome in the Korean Longitudinal Study on Health and Aging (KLoSHA). *Diabetes Care*. 2010;33:1652-1654.
28. Carlsen RC, Gray SD. Decline of isometric force and fatigue resistance in skeletal muscles from spontaneously hypertensive rats. *Exp Neurol*. 1987;95:249-264.
29. Coelho-Junior HJ, Gambassi BB, Irigoyen MC, et al. Hypertension, sarcopenia, and global cognitive function in community-dwelling older women: a preliminary study. *J Aging Res*. 2018;2018:9758040.
30. Burrows R, Correa-Burrows P, Reyes M, Blanco E, Albala C, Gahagan S. Low muscle mass is associated with cardiometabolic risk regardless of nutritional status in adolescents: A cross-sectional study in a Chilean birth cohort. *Pediatr Diabetes*. 2017;18:895-902.
31. Santulli G, Ciccarelli M, Trimarco B, Iaccarino G. Physical activity ameliorates cardiovascular health in elderly subjects: the functional role of the beta adrenergic system. *Front Physiol*. 2013;4:209.
32. MacDonald HV, Johnson BT, Huedo-Medina TB, et al. Dynamic resistance training as stand-alone antihypertensive lifestyle therapy: a meta-analysis. *J Am Heart Assoc*. 2016;5:e003231.
33. Ciccarelli M, Sorriento D, Coscioni E, Iaccarino G, Santulli G. Adrenergic receptors. In: Schisler J, Lang C, Willis M, eds. *Endocrinology of the Heart in Health and Disease*. London, UK: Academic Press; 2017:285–315.
34. Lopes AA, James SA, Port FK, Ojo AO, Agodoa LY, Jamerson KA. Meeting the challenge to improve the treatment of hypertension in blacks. *J Clin Hypertens (Greenwich)*. 2003;5:393–401.
35. Izzo R, Cipolletta E, Ciccarelli M, et al. Enhanced GRK2 expression and desensitization of betaAR vasodilatation in hypertensive patients. *Clin Transl Sci*. 2008;1:215–220.
36. Paula TP, Viana LV, Neto A, Leitão CB, Gross JL, Azevedo MJ. Effects of the DASH diet and walking on blood pressure in patients with type 2 diabetes and uncontrolled hypertension: a randomized controlled trial. *J Clin Hypertens (Greenwich)*. 2015;17:895–901.

37. Hittel DS, Berggren JR, Shearer J, Boyle K, Houmard JA. Increased secretion and expression of myostatin in skeletal muscle from extremely obese women. *Diabetes*. 2009;58:30–38.
38. McPherron AC, Lee SJ. Suppression of body fat accumulation in myostatin-deficient mice. *J Clin Invest*. 2002;109:595–601.
39. Butcher JT, Mintz JD, Larion S, et al. Increased muscle mass protects against hypertension and renal injury in obesity. *JAHA*. 2018;7.
40. Ervin RB. Prevalence of metabolic syndrome among adults 20 years of age and over, by sex, age, race and ethnicity, and body mass index: United States, 2003–2006. *Natl Health Stat Report*. 2009;13:1–7.
41. Gómez-Ambrosi J, Silva C, Galofré JC, et al. Body adiposity and type 2 diabetes: increased risk with a high body fat percentage even having a normal BMI. *Obesity (Silver Spring)*. 2011;19:1439–1444.
42. Zhao T, Lin Z, Zhu H, Wang C, Jia W. Impact of body fat percentage change on future diabetes in subjects with normal glucose tolerance. *IUBMB Life*. 2017;69:947–955.
43. Meisinger C, Doring A, Thorand B, Heier M, Lowel H. Body fat distribution and risk of type 2 diabetes in the general population: are there differences between men and women? The MONICA/KORA Augsburg cohort study. *Am J Clin Nutr*. 2006;84:483–489.
44. Vikram NK, Pandey RM, Misra A, Sharma R, Devi JR, Khanna N. Non-obese (body mass index < 25 kg/m2) Asian Indians with normal waist circumference have high cardiovascular risk. *Nutrition*. 2003;19:503–509.
45. Jo A, Mainous AG 3rd. Informational value of percent body fat with body mass index for the risk of abnormal blood glucose: a nationally representative cross-sectional study. *BMJ Open*. 2018;8:e019200.
46. Mainous AG 3rd, Tanner RJ, Jo A, Anton SD. Prevalence of prediabetes and abdominal obesity among healthy-weight adults: 18-year trend. *Ann Fam Med*. 2016;14:304–310.
47. Mainous AG 3rd, Tanner RJ, Anton SD, Jo A, Luetke MC. Physical activity and abnormal blood glucose among healthy weight adults. *Am J Prev Med*. 2017;53:42–47.
48. Tokodai K, Amada N, Kikuchi H, Haga I, Takayama T, Nakamura A. Body fat percentage as a marker of new-onset diabetes mellitus after kidney transplantation. *Transplant Proc*. 2013;45:1544–1547.
49. Lombardi A, Gambardella J, Du X-L, et al. Sirolimus induces depletion of intracellular calcium stores and mitochondrial dysfunction in pancreatic beta cells. *Sci Rep*. 2017;7:15823.
50. Lombardi A, Trimarco B, Iaccarino G, Santulli G. Impaired mitochondrial calcium uptake caused by tacrolimus underlies beta-cell failure. *Cell Commun Signal*. 2017;15:47.
51. Gambardella J, Santulli G. Integrating diet and inflammation to calculate cardiovascular risk. *Atherosclerosis*. 2016;253:258–261.
52. Danaei G, Lawes CM, Vander Hoorn S, Murray CJ, Ezzati M. Global and regional mortality from ischaemic heart disease and stroke attributable to higher-than-optimum blood glucose concentration: comparative risk assessment. *Lancet*. 2006;368:1651–1659.
53. Morisco C, Lembo G, Trimarco B. Insulin resistance and cardiovascular risk: New insights from molecular and cellular biology. *Trends Cardiovasc Med*. 2006;16:183–188.
54. Shu J, Santulli G. Update on peripheral artery disease: Epidemiology and evidence- based facts. *Atherosclerosis*. 2018;275:379–381.
55. Gress TW, Nieto FJ, Shahar E, Wofford MR, Brancati FL. Hypertension and antihypertensive therapy as risk factors for type 2 diabetes mellitus. Atherosclerosis risk in communities study. *N Engl J Med*. 2000;342:905–912.
56. Chokshi NP, Grossman E, Messerli FH. Blood pressure and diabetes: vicious twins. *Heart*. 2013;99:577–585.
57. Ferrannini E, Cushman WC. Diabetes and hypertension: the bad companions. *Lancet*. 2012;380:601–610.
58. Izzo R, de Simone G, Chinali M, et al. Insufficient control of blood pressure and incident diabetes. *Diabetes Care*. 2009;32:845–850.
59. Izzo R, de Simone G, Trimarco V, et al. Hypertensive target organ damage predicts incident diabetes mellitus. *Eur Heart J*. 2013;34:3419–3426.
60. Muniyappa R, Montagnani M, Koh KK, Quon MJ. Cardiovascular actions of insulin. *Endocr Rev*. 2007;28:463–491.