Making sense of subclinical cardiac alterations in patients with diabetes

Manan Pareek[1,2*], Michael Hecht Olsen[3]

[1]Department of Cardiology, North Zealand Hospital, Hillerød, Denmark, [2]Department of Internal Medicine, Yale New Haven Hospital, Yale University School of Medicine, New Haven, Connecticut, USA, [3]Department of Internal Medicine, Division of Cardiology, Holbaek Hospital, Holbaek, Denmark

DOI: http://dx.doi.org/10.17305/bjbms.2019.4349 *Bosn J Basic Med Sci. 2019;19(4):312-314. © 2019 ABMSFBIH*

Patients with diabetes are prone to develop a distinct primary myocardial condition, diabetic cardiomyopathy, placing them at an increased risk for heart failure [1-3]. This occurs independently of hypertension, coronary artery disease, and other established causes of heart failure. Pertinent findings include increased mass, concentric changes, and diastolic dysfunction of the left ventricle [4,5]. Such adverse remodeling is common among patients with diabetes and appears to be strongly associated with its duration, suggesting a role for persistent metabolic stress [6-8]. However, which exact components of the diabetic syndrome determine these cardiac alterations is not clear. Moreover, most studies have investigated patients with type 2 diabetes, and it is uncertain whether patients with type 1 diabetes experience similar myocardial changes.

In keeping with this knowledge gap, the recently published study by Šuran et al. examined cross-sectional associations between markers of left ventricular structure and function and easily obtained anthropometric and laboratory variables, among patients with type 1 diabetes [9]. Sixty-one study participants with a mean age of ~44 years and mean body mass index ~27 kg/m^2, without manifest cardiovascular disease or hypertension, and with a duration of diabetes >5 years (mean ~18 years) were consecutively included. Patients with chronic kidney disease stage ≥G2 or gross echocardiographic abnormalities were excluded. The investigators found body mass index to be moderately correlated with various markers of cardiac structure and diastolic function (Figure 1). Body mass index remained significantly associated with left ventricular mass, left atrial volume, left ventricular end-diastolic diameter, and E/A after accounting for age, diabetes duration, and average glycated hemoglobin (HbA1c) during the last 5 years. On the other hand, variables like fasting serum glucose, diabetes duration, and HbA1c did not, for the most part, demonstrate relations with echocardiographic measures. The authors concluded that overweight and obese patients with type 1 diabetes may be particularly prone to developing cardiomyopathy.

While the lack of robust associations between glycemic abnormalities and adverse left ventricular remodeling may be unexpected, results regarding this relationship have not been entirely consistent and appear to depend on the characteristics of the study participants. For example, a cross-sectional study of 693 apparently healthy individuals (median age 66 years) derived from the Swedish Malmö Preventive Project found body mass index, but not fasting plasma glucose, to be linked with left ventricular mass and left ventricular hypertrophy [10]. Body mass index was not associated with diastolic function, although that may have been caused by the inclusion of left ventricular mass index in the multivariable analyses [11]. In a subgroup of 247 men (median age 47 years), body mass index was an independent predictor of future left ventricular mass and diastolic function, while insulin sensitivity was not [12]. Curiously, a Japanese cross-sectional study of 145 patients with type 2 diabetes who were matched with 90 healthy controls showed that body mass index ≥25 kg/m^2 only predicted lower global longitudinal strain among those with diabetes [13,14]. Still, HbA1c was not independently associated with global longitudinal strain.

A proper discussion of type 1 diabetes inevitably requires mention of the Danish Thousand & 1 study [15]. Jensen et al. examined 1093 patients with type 1 diabetes (mean age ~50 years) without known heart disease and with a mean diabetes duration of 25.5 years, 15.5% of whom displayed grossly abnormal systolic or diastolic findings. In the primary report, diabetes duration was significantly associated with echocardiographic alterations [15]. In contrast, HbA1c was not associated with a pathological echocardiogram, but albuminuria, whether of the micro or macro subtype, was a powerful predictor

*Corresponding author: Manan Pareek, Department of Cardiology, North Zealand Hospital, Dyrehavevej 29, 3400 Hillerød, Denmark. Phone: +45-25-53-69-00. E-mail: mananpareek@dadlnet.dk

Submitted: 06 July 2019/Accepted: 06 July 2019

thereof. Individual Doppler-echocardiographic indices of diastolic function were impaired among patients with diabetes versus those without, regardless of albuminuria [16], though remarkably, global longitudinal strain only differed from healthy controls among those with albuminuria [17]. Accordingly, a fair portion of the heterogeneity between studies could also be attributed to the specific echocardiographic measures that are tested, particularly since they may display complex, non-linear associations with actual myocardial function [18,19].

Finally, the different phenotypes within each diabetic entity may limit direct comparisons [20]. In other words, type 2 diabetes is not just type 2 diabetes, and type 1 diabetes is not simply type 1 diabetes as exemplified by the Thousand & 1 study. Insulin resistance, hyperinsulinemia, obesity, hypertension, and diabetes also frequently co-occur, making it difficult to assess the separate role of each of these conditions in developing structural and functional cardiac alterations [21-23]. However, as Šuran et al. also suggested, hyperglycemia may primarily exert its effects by increasing the susceptibility of the heart to other adverse stimuli [9]. This complies with the classical concept of a cardiovascular continuum, whereby both physiological aging and pathological aging due to cardiovascular risk factors such as diabetes result in similar disturbances in left ventricular structure and function [24-26]. Indeed, in the Thousand & 1 study, those with diabetes developed adverse echocardiographic changes at a much earlier age than would otherwise be expected [16]. As such, hyperglycemia may also modify the relationship between body mass index and cardiovascular disease. Adding to this the fact that postload glucose may better predict cardiovascular morbidity and mortality than fasting glucose [27], one may have a possible explanation of why body mass index appears to be more consistently associated with abnormal echocardiography than do fasting glucose and HbA1c [28]. Other, simpler explanations

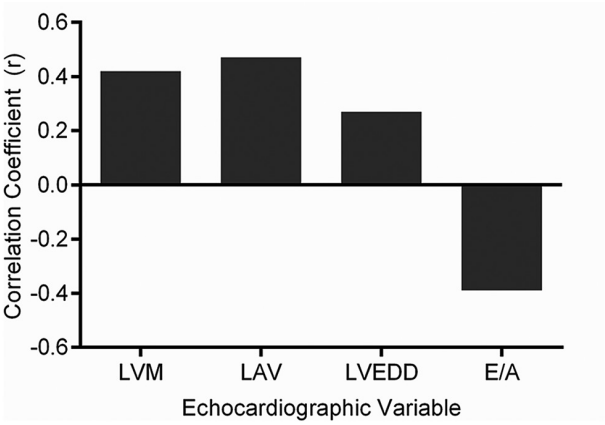

FIGURE 1. Select correlation coefficients between body mass index and echocardiographic variables of the left ventricle in the study by Šuran et al. [9]. LVM: Left ventricular mass, LAV: Left atrial volume, LVEDD: Left ventricular end-diastolic diameter.

for the lack of associations in the present, hypothesis-generating study may include the study participant homogeneity, including the exclusion of patients with known cardiovascular disease, and limited sample size (type 2 error). Additionally, the apparent associations with body mass index might have been exaggerated by the fact that, for these particular analyses, the echocardiographic variables were not indexed for body surface area or allometrically scaled, e.g., by height[1,7].

In conclusion, the findings reported by Šuran et al. are thought-provoking and add to the notion that optimal treatment of patients with diabetes and subclinical cardiac damage may require targeting of multiple, interrelated pathways. Future studies should focus on whether weight loss and non-insulin therapy, e.g., sodium-glucose cotransporter-2 inhibitors, among patients with type 1 diabetes and overweight or obesity may improve myocardial function [29,30]. Lastly, it remains to be determined how these patients should be monitored and whether particular subgroups may benefit from echocardiographic surveillance.

DECLARATION OF INTERESTS

Dr. Manan Pareek discloses the following relationships – Advisory Board: AstraZeneca; Speaker's Fee: AstraZeneca, Bayer, Boehringer Ingelheim. Dr. Michael Hecht Olsen discloses that he has received a part-time clinical research grant from the Novo Nordisk Foundation.

REFERENCES

[1] Grundy SM, Benjamin IJ, Burke GL, Chait A, Eckel RH, Howard BV, et al. Diabetes and cardiovascular disease: A statement for healthcare professionals from the American Heart Association. Circulation 1999;100:1134-46. https://doi.org/10.1161/01.cir.100.10.1134.

[2] Pareek M, Vaduganathan M, Bhatt DL, Leósdóttir M, Olsen MH. Prognostic implications of fasting plasma glucose in subjects with echocardiographic abnormalities. Int J Cardiol 2017;241:423-9. https://doi.org/10.1016/j.ijcard.2017.01.133.

[3] Jørgensen PG, Biering-Sørensen T, Mogelvang R, Fritz-Hansen T, Vilsbøll T, Rossing P, et al. Predictive value of echocardiography in type 2 diabetes. Eur Heart J Cardiovasc Imaging 2019;20:687-93. https://doi.org/10.1093/ehjci/jey164.

[4] Boudina S, Abel ED. Diabetic cardiomyopathy revisited. Circulation 2007;115:3213-23. https://doi.org/10.1161/circulationaha.106.679597.

[5] Pareek M. The interplay between fasting glucose, echocardiography, and biomarkers: Pathophysiological considerations and prognostic implications. Dan Med J 2017;64:B5400.

[6] From AM, Scott CG, Chen HH. Changes in diastolic dysfunction in diabetes mellitus over time. Am J Cardiol 2009;103:1463-6. https://doi.org/10.1016/j.amjcard.2009.01.358.

[7] Jørgensen PG, Jensen MT, Mogelvang R, Fritz-Hansen T, Galatius S, Biering-Sørensen T, et al. Impact of type 2 diabetes and duration of type 2 diabetes on cardiac structure and function. Int J Cardiol 2016;221:114-21. https://doi.org/10.1016/j.ijcard.2016.07.083.

[8] Jørgensen PG, Jensen MT, Mogelvang R, von Scholten BJ, Bech J, Fritz-Hansen T, et al. Abnormal echocardiography in patients with

type 2 diabetes and relation to symptoms and clinical characteristics. Diab Vasc Dis Res 2016;13:321-30. https://doi.org/10.1177/1479164116645583.
[9] Šuran D, Kanič V, Naji F, Krajnc I, Čokolič M, Zemljič E, et al. Predictors of early cardiac changes in patients with type 1 diabetes mellitus: An echocardiography-based study. Bosn J Basic Med Sci 2019. [Epub ahead of print] https://doi.org/10.17305/bjbms.2019.4250.
[10] Pareek M, Aharaz A, Nielsen ML, Gerke O, Leósdóttir M, Møller JE, et al. Untreated diabetes mellitus, but not impaired fasting glucose, is associated with increased left ventricular mass and concentric hypertrophy in an elderly, healthy, Swedish population. IJC Metab Endocr 2015;9:39-47. https://doi.org/10.1016/j.ijcme.2015.10.005.
[11] Pareek M, Nielsen ML, Gerke O, Leósdóttir M, Møller JE, Hindersson P, et al. Worsening diastolic function is associated with elevated fasting plasma glucose and increased left ventricular mass in a supra-additive fashion in an elderly, healthy, Swedish population. Int J Cardiol 2015;184:466-72. https://doi.org/10.1016/j.ijcard.2015.03.037.
[12] Nielsen ML, Pareek M, Gerke O, Leósdóttir M, Nilsson PM, Olsen MH, et al. Greater body mass index is a better predictor of subclinical cardiac damage at long-term follow-up in men than is insulin sensitivity: A prospective, population-based cohort study. BMC Cardiovasc Disord 2015;15:168. https://doi.org/10.1186/s12872-015-0165-3.
[13] Suto M, Tanaka H, Mochizuki Y, Mukai J, Takada H, Soga F, et al. Impact of overweight on left ventricular function in type 2 diabetes mellitus. Cardiovasc Diabetol 2017;16:145. https://doi.org/10.1186/s12933-017-0632-5.
[14] Musaeus KD, Pareek M. Body mass index, type 2 diabetes, and left ventricular function. Cardiovasc Diabetol 2018;17:3. https://doi.org/10.1186/s12933-017-0649-9.
[15] Jensen MT, Sogaard P, Andersen HU, Bech J, Hansen TF, Galatius S, et al. Prevalence of systolic and diastolic dysfunction in patients with type 1 diabetes without known heart disease: The Thousand and 1 Study. Diabetologia 2014;57:672-80. https://doi.org/10.1007/s00125-014-3164-5.
[16] Jensen MT, Sogaard P, Andersen HU, Gustafsson I, Bech J, Hansen TF, et al. Early myocardial impairment in type 1 diabetes patients without known heart disease assessed with tissue Doppler echocardiography: The Thousand and 1 Study. Diab Vasc Dis Res 2016;13:260-7. https://doi.org/10.1177/1479164116637310.
[17] Jensen MT, Sogaard P, Andersen HU, Bech J, Hansen TF, Biering-Sørensen T, et al. Global longitudinal strain is not impaired in type 1 diabetes patients without albuminuria: The Thousand and 1 Study. JACC Cardiovasc Imaging 2015;8:400-10. https://doi.org/10.1016/j.jcmg.2014.12.020.
[18] Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. J Am Soc Echocardiogr 2009;22:107-33. https://doi.org/10.1016/j.echo.2008.11.023.
[19] Nagueh SF, Smiseth OA, Appleton CP, Byrd BF 3rd, Dokainish H, Edvardsen T, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: An update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2016;29:277-314. https://doi.org/10.1016/j.echo.2016.01.011.
[20] Stidsen JV, Henriksen JE, Olsen MH, Thomsen RW, Nielsen JS, Rungby J, et al. Pathophysiology-based phenotyping in type 2 diabetes: A clinical classification tool. Diabetes Metab Res Rev 2018;34:e3005. https://doi.org/10.1002/dmrr.3005.
[21] Galvan AQ, Galetta F, Natali A, Muscelli E, Sironi AM, Cini G, et al. Insulin resistance and hyperinsulinemia: No independent relation to left ventricular mass in humans. Circulation 2000;102:2233-8. https://doi.org/10.1161/01.cir.102.18.2233.
[22] Rutter MK, Parise H, Benjamin EJ, Levy D, Larson MG, Meigs JB, et al. Impact of glucose intolerance and insulin resistance on cardiac structure and function: Sex-related differences in the Framingham Heart Study. Circulation 2003;107:448-54. https://doi.org/10.1161/01.cir.0000045671.62860.98.
[23] Jørgensen PG, Jensen MT, Biering-Sørensen T, Mogelvang R, Fritz-Hansen T, Vilsbøll T, et al. Burden of uncontrolled metabolic risk factors and left ventricular structure and function in patients with type 2 diabetes mellitus. J Am Heart Assoc 2018;7:e8856. https://doi.org/10.1161/jaha.118.008856.
[24] Dzau VJ, Antman EM, Black HR, Hayes DL, Manson JE, Plutzky J, et al. The cardiovascular disease continuum validated: Clinical evidence of improved patient outcomes: Part I: Pathophysiology and clinical trial evidence (risk factors through stable coronary artery disease). Circulation 2006;114:2850-70. https://doi.org/10.1161/circulationaha.106.655688.
[25] Dzau VJ, Antman EM, Black HR, Hayes DL, Manson JE, Plutzky J, et al. The cardiovascular disease continuum validated: Clinical evidence of improved patient outcomes: Part II: Clinical trial evidence (acute coronary syndromes through renal disease) and future directions. Circulation 2006;114:2871-91. https://doi.org/10.1161/circulationaha.106.655761.
[26] O'Rourke MF, Safar ME, Dzau V. The cardiovascular continuum extended: Aging effects on the aorta and microvasculature. Vasc Med 2010;15:461-8. https://doi.org/10.1177/1358863x10382946.
[27] Unwin N, Shaw J, Zimmet P, Alberti KG. Impaired glucose tolerance and impaired fasting glycaemia: The current status on definition and intervention. Diabet Med 2002;19:708-23. https://doi.org/10.1046/j.1464-5491.2002.00835.x.
[28] Pareek M, Vaduganathan M, Bhatt DL, Olsen MH. Reply: Intersection of fasting plasma glucose, adverse cardiac remodeling, and clinical outcomes. Int J Cardiol 2018;252:214-5. https://doi.org/10.1016/j.ijcard.2017.11.048.
[29] Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Bonaca MP, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: A systematic review and meta-analysis of cardiovascular outcome trials. Lancet 2019;393:31-9. https://doi.org/10.1016/s0140-6736(18)32590-x.
[30] Natali A, Nesti L, Fabiani I, Calogero E, Di Bello V. Impact of empagliflozin on subclinical left ventricular dysfunctions and on the mechanisms involved in myocardial disease progression in type 2 diabetes: Rationale and design of the EMPA-HEART trial. Cardiovasc Diabetol 2017;16:130. https://doi.org/10.1186/s12933-017-0615-6.

Related articles published in BJBMS

1. Predictors of early cardiac changes in patients with type 1 diabetes mellitus: An echocardiography-based study
   David Šuran et al., BJBMS, 2019
2. Effect and mechanisms of zinc supplementation in protecting against diabetic cardiomyopathy in a rat model of type 2 diabetes
   Ying Lu et al., BJBMS, 2015
3. Effects of hyperglycemia and iron deficiency on kidney and heart function in type 2 diabetes disease
   Belma Aščić-Buturović et al., BJBMS, 2006
4. Cystatin C as a marker for detection of early renal failure in diabetes type 2 patients
   Belma Aščić-Buturović et al., BJBMS, 2005