and association with micro and macrovascular complications. Diabet Med 2015;32:90–6.
[3] Borel AL, Benhamou PY, Baguet JP, Halimi S, Levy P, Mallion JM, et al. High prevalence of obstructive sleep apnoea syndrome in a Type 1 diabetic adult population: a pilot study. Diabet Med 2010;27:1328–9.
[4] Schober AK, Neurath MF, Harsch IA. Prevalence of sleep apnoea in diabetic patients. Clin Respir J 2011;5:165–72.
[5] Selvarajah D, Cash T, Davies J, Sankar A, Rao G, Grieg M, et al. SUDOSCAN: a simple, rapid, and objective method with potential for screening for diabetic peripheral neuropathy. PLoS One 2015;10:e138224.
[6] Catterall JR, Calverley PMA, Ewing DJ, Shapiro CM, Clarke BF, Douglas NJ. Breathing, sleep, and diabetic autonomic neuropathy. Diabetes 1984;33:1025–7.
[7] Neumann C, Martinez D, Schmid H. Nocturnal oxygen desaturation in diabetic patients with severe autonomic neuropathy. Diab Res Clin Pract 1995;28:97–102.
[8] Ficker JH, Dertinger SH, Siegfried W, König HJ, Pentz M, Sailer D, et al. Obstructive sleep apnoea and diabetes mellitus: the role of cardiovascular autonomic neuropathy. Eur Respir J 1998;11:14–9.
[9] Bottini P, Scionti L, Santeusanio F, Casucci G, Tantucci C. Impairment of the respiratory system in diabetic autonomic neuropathy. Diabetes Nutr Metab 2000;13:165–72.
[10] Janovsky CC, Rolim LC, de Sà JR, Poyares D, Tufik S, Silva AB, et al. Cardiovascular autonomic neuropathy contributes to sleep apnea in young and lean type 1 diabetes mellitus patients. Front Endocrinol (Lausanne) 2014;5:119.

L. Meyer[a,*], M. Massuyeau[a], C. Canel[a], T. Bahougne[a], P. Assemi[b], A.-E. Perrin[b], E. Wurtz[b], B. Renaud-Picard[a], C. Iamandi[c], R. Kessler[a], L. Kessler[a]

[a] *Endocrinology, hôpitaux universitaires de Strasbourg, 1, place de l'Hôpital, Bas-Rhin, 67091 Strasbourg, France*
[b] *Centre hospitalier de Saverne, 67700 Saverne, France*
[c] *Centre hospitalier de Mulhouse, 68100 Mulhouse, France*

[*] Corresponding author
E-mail address: laurent.meyer@chru-strasbourg.fr (L. Meyer).

Received 19 July 2017
Received in revised form 22 October 2017
Accepted 23 October 2017
Available online 7 November 2017

https://doi.org/10.1016/j.diabet.2017.10.011

Association of handgrip strength with B-type natriuretic peptide levels and cardiovascular events in patients with type 2 diabetes

B-type natriuretic peptide (BNP) is a useful predictor of cardiovascular (CV) events and death in patients with heart failure [1,2]. BNP is also a powerful predictive marker of CV events beyond heart failure and death in patients with type 2 diabetes (T2D) [3]. Previous studies have shown that, in healthy individuals, exercise induces BNP secretion, which may have cytoprotective effects on the heart [4]. In addition, recent studies have shown that natriuretic peptides, including BNP, play a role in lipid oxidation in fat tissue and in enhancing oxidative capacity in skeletal muscle [4]. Handgrip exercise increases BNP levels by 30% in healthy men [5], while moderate-intensity walking increases BNP levels in patients with cardiovascular disease (CVD), but not in healthy people or in patients with CV risk factors [6]. In contrast, low-intensity daily physical activity is associated with an increase in BNP levels in patients with T2D [7]. However, the association between exercise and BNP levels may change depending on the disease/condition or level of physical fitness. Yamashita et al. [8] showed that muscle mass measured by cross-sectional area of thigh muscle was negatively associated with plasma BNP levels in healthy people. However, no researcher has investigated the association of handgrip strength, a simple and useful method for evaluating muscle strength, with BNP levels and CV events in patients with T2D. Thus, the present study aimed to examine those associations in such patients.

This retrospective cohort study was conducted in T2D patients treated at the National Center for Global Health and Medicine, Kohnodai Hospital. Between April 2013 and December 2015, outpatients whose handgrip strength and plasma BNP levels were measured at the same time were included. Patients were instructed to consume a calorie-restricted diet of 25–30 kcal/kg (ideal body weight)/day as dietary therapy for diabetes by certified nutritional educators, and to continue the diet throughout the study period. CV events included stroke and non-fatal coronary heart disease.

The study protocol was approved by the Medical Ethics Committee of the National Center for Global Health and Medicine (Reference No. NCGM-G-002052), and the study was performed in accordance with the Declaration of Helsinki.

Height was measured using a rigid stadiometer (Tsutsumi Co., Ltd., Tokyo, Japan). Weight was measured using calibrated scales (AD-6107NW; A&D Company Limited, Tokyo, Japan). Body mass index (BMI) was calculated as body weight in kg divided by height in m^2. Blood pressure was measured in a sitting position using an automatic sphygmomanometer (HBP-9020; Omron Healthcare Co., Ltd., Kyoto, Japan).

Handgrip strength was measured in each hand using a Smedley analogue hand dynamometer (No. 04125; MIS, Tokyo, Japan) in standing position. Measurements were taken of the dominant hand first. Subjects performed a maximum of two attempts for each hand with an approximately 1-min rest period in between, and their average handgrip strength was calculated in kg. Patients were also asked about their regular exercise habits, and their daily exercise times were calculated using a questionnaire.

Blood samples were drawn in the morning from an antecubital vein. Plasma glucose, haemoglobin A_{1c} (HbA_{1c}) and BNP levels were measured. Plasma BNP levels were measured using a specific immunoradiometric assay for human BNP (Architect BNP-JP®, Abbott Japan Co., Ltd., Tokyo, Japan). Estimated glomerular filtration rate (eGFR) was calculated using the revised equation adjusted for the Japanese population [9].

Statistical analyses were performed using SPSS version 24 software (IBM Corp., Armonk, NY, USA). All values were expressed as means ± standard deviation (SD). Multiple regression analysis, adjusted for age, gender, BMI, exercise time, systolic blood

Table 1
Clinical characteristics of subjects with type 2 diabetes.

	Mean ± SD
Demographic data	
Age (years)	64.7 (14.1)
Gender (males/females)	253/183[a]
Exercise time (min/day)	16.1 (9.1)
Duration of diabetes (years)	11.8 (11.6)
Anthropometric data	
Height (cm)	160.4 (9.9)
Weight (kg)	66 (17.5)
Body mass index (kg/m²)	25.4 (5.8)
Handgrip strength (kg)	23.4 (9.9)
Physiological and biochemical data	
Systolic blood pressure (mmHg)	135.5 (21.9)
Diastolic blood pressure (mmHg)	75.4 (14.9)
Plasma glucose (mg/dL)	179.5 (73.9)
HbA_{1c} (%)	8.2 (2)
Estimated glomerular filtration rate (mL/min/1.73 m²)	72.7 (27.4)
Plasma B-type natriuretic peptide	44.9 (105.9)

[a] *n*/*n*.

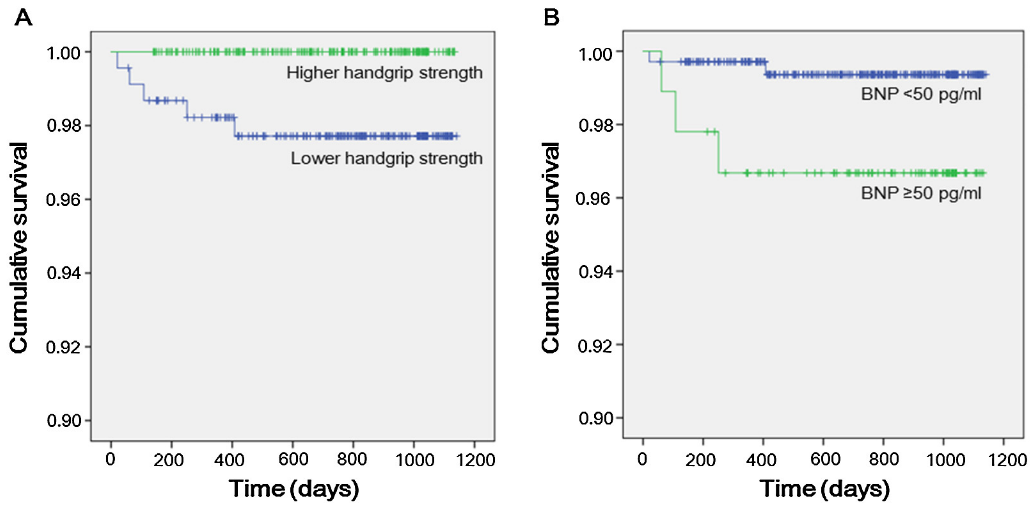

Fig. 1. Kaplan–Meier survival analyses of handgrip strength and plasma B-type natriuretic peptide (BNP) levels in relation to cardiovascular events: (A) subjects were divided into higher and lower muscle strength groups on either side of the median (28.375 kg for men and 16.0 kg for women); and (B) subjects were divided into groups of lower ($<$ 50 pg/mL) and higher ($\geq$ 50 pg/mL) BNP levels.

pressure, eGFR and HbA_{1c}, was performed to test independent associations between handgrip strength and BNP levels. In addition, the Kaplan–Meier curve for survival analysis was performed, with the difference assessed by log-rank test. The entry variable was the date of measurement of handgrip strength and BNP. Follow-up was censored at the time of the first CV event, death or 1 May 2016, whichever came first. A P value < 0.05, determined by a two-sided test, was considered statistically significant.

The present study enrolled 436 patients (253 men and 183 women) with T2D. The mean age of study participants was 64.7 ± 14.1 years, and the mean BMI was 25.4 ± 5.8 kg/m^2. Characteristics of the subjects at baseline are presented in Table 1.

Multiple regression analysis revealed that handgrip strength was inversely associated with plasma BNP levels ($\beta = -0.086$, $P = 0.014$). Over a mean follow-up of 762 ± 292 days, five patients (1.1%) died and five (1.1%) experienced CV events. Kaplan–Meier survival analysis confirmed the negative association between handgrip strength and risk of CV events ($P = 0.034$), and the positive association with BNP levels ($P = 0.033$; Fig. 1).

The present study demonstrates that handgrip strength was inversely associated with plasma BNP levels in addition to being a predictor of CV events in Japanese patients with T2D. To my knowledge, this is the first-ever study to report a significant association between handgrip strength and BNP in a T2D population.

Handgrip strength is useful for diagnosing sarcopenia [10], and has been identified as an indicator of mortality and CVD risk in patients with diabetes [11], and BNP is a prognostic marker of CV morbidity and mortality in T2D patients [3]. Findings of this study also indicate that decreased handgrip strength and increased BNP levels are associated with CV events. Although the underlying mechanism is still not fully understood, the link between skeletal muscle and BNP has been investigated. Onoue et al. [12] demonstrated that circulating BNP levels are significantly higher in sarcopenic patients with heart failure. Skeletal muscle has been identified as an endocrine organ that secretes myokines that have a favourable impact on metabolism [13]. For example, irisin increases myocardial cell metabolism, decreases cell proliferation and promotes cell differentiation [14]. Fibroblast growth factor 21 increases levels of adiponectin, known to be a cardioprotective adipokine, and attenuates cardiac remodelling after myocardial infarction [15]. Myokines hold the promise of cardioprotective effects. Certainly, T2D patients with decreased handgrip strength may be physically weak, suffer from comorbidities including heart failure and have increased plasma BNP levels; in contrast, it is possible that increased muscle strength exerts cardioprotective effect *via* secretion of myokines and also reduces BNP levels.

This study has a couple of limitations. First, cardiac function in the study subjects was not evaluated and, therefore, the results may be confounded by baseline heart function. Second, the study design cannot deduce a causal relationship between handgrip strength and BNP. To elucidate the association between muscle strength and BNP, further prospective studies are warranted.

In conclusion, the present study suggests that both handgrip strength and plasma BNP levels are predictive of CV events in patients with T2D. Skeletal muscle weakness may cause a metabolic disturbance in skeletal muscle as well as in the rest of the body, thereby affecting cardiac load and, consequently, increasing plasma BNP levels.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

Disclosure of interest

The author declares that he has no competing interest.

Acknowledgments

The author appreciates the support of the Clinical Research Center at the National Center for Global Health and Medicine, Kohnodai Hospital.

References

[1] Berger R, Huelsman M, Strecker K, Bojic A, Moser P, Stanek B, et al. B-type natriuretic peptide predicts sudden death in patients with chronic heart failure. Circulation 2002;105:2392–7.
[2] Wang TJ, Larson MG, Levy D, Benjamin EJ, Leip EP, Omland T, et al. Plasma natriuretic peptide levels and the risk of cardiovascular events and death. N Engl J Med 2004;350:655–63.
[3] Wolsk E, Claggett B, Pfeffer MA, Diaz R, Dickstein K, Gerstein HC, et al. Role of B-type natriuretic peptide and N-terminal prohormone BNP as predictors of cardiovascular morbidity and mortality in patients with a recent coronary event and type 2 diabetes mellitus. J Am Heart Assoc 2017;6.

[4] Hamasaki H. The effects of exercise on natriuretic peptides in individuals without heart failure. Sports 2016;4:32.
[5] Barletta G, Stefani L, Del Bene R, Fronzaroli C, Vecchiarino S, Lazzeri C, et al. Effects of exercise on natriuretic peptides and cardiac function in man. Int J Cardiol 1998;65:217–25.
[6] Aengevaeren VL, Hopman MT, Thijssen DH, van Kimmenade RR, de Boer MJ, Eijsvogels TM. Endurance exercise-induced changes in BNP concentrations in cardiovascular patients versus healthy controls. Int J Cardiol 2017;227:430–5.
[7] Hamasaki H, Yanai H, Kakei M, Noda M, Ezaki O. The association between daily physical activity and plasma B-type natriuretic peptide in patients with glucose intolerance: a cross-sectional study. BMJ Open 2015;5:e006276.
[8] Yamashita T, Kohara K, Tabara Y, Ochi M, Nagai T, Okada Y, et al. Muscle mass, visceral fat, and plasma levels of B-type natriuretic peptide in healthy individuals (from the J-SHIPP Study). Am J Cardiol 2014;114:635–40.
[9] Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, et al. Collaborators developing the Japanese equation for estimated GFR. Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis 2009;53:982–92.
[10] Roberts HC, Denison HJ, Martin HJ, Patel HP, Syddall H, Cooper C, et al. A review of the measurement of grip strength in clinical and epidemiological studies: towards a standardised approach. Age Ageing 2011;40:423–49.
[11] Lopez-Jaramillo P, Cohen DD, Gómez-Arbeláez D, Bosch J, Dyal L, Yusuf S, et al. Association of handgrip strength to cardiovascular mortality in pre-diabetic and diabetic patients: a subanalysis of the ORIGIN trial. Int J Cardiol 2014;174:458–61.
[12] Onoue Y, Izumiya Y, Hanatani S, Tanaka T, Yamamura S, Kimura Y, et al. A simple sarcopenia screening test predicts future adverse events in patients with heart failure. Int J Cardiol 2016;215:301–6.
[13] Pedersen BK, Febbraio MA. Muscles, exercise and obesity: skeletal muscle as a secretory organ. Nat Rev Endocrinol 2012;8:457–65.
[14] Xie C, Zhang Y, Tran TD, Wang H, Li S, George EV, et al. Irisin controls growth, intracellular Ca2+ signals, and mitochondrial thermogenesis in cardiomyoblasts. PLoS One 2015;10:e0136816.
[15] Joki Y, Ohashi K, Yuasa D, Shibata R, Ito M, Matsuo K, et al. FGF21 attenuates pathological myocardial remodeling following myocardial infarction through the adiponectin-dependent mechanism. Biochem Biophys Res Commun 2015;459:124–30.

H. Hamasaki[a,b,*]
[a] *Hamasaki Clinic, Kagoshima, Japan*
[b] *Department of Internal Medicine, National Centre for Global Health and Medicine Kohnodai Hospital, Chiba, Japan*

[*] 2-21-4 Nishida, 890-0046 Kagoshima, Japan.
Fax: +81 99 2501470
E-mail address: hhamasaki78@gmail.com

Received 19 June 2017
Received in revised form 29 June 2017
Accepted 2 July 2017
Available online 24 July 2017

https://doi.org/10.1016/j.diabet.2017.07.001