Relationship between Metformin and Frailty Syndrome in Elderly People with Type 2 Diabetes

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ABSTRAK

Tujuan: untuk mempelajari apakah ada efek protektif metformin terhadap sindrom frailty. *Metode:* studi dilakukan secara kasus kontrol pada subyek berusia ≥60 tahun yang berobat di poliklinik geriatri dan diabetes FKUI-RSCM, bulan Maret-Juni 2013. Diagnosis frailty ditegakkan menggunakan indeks frailty-40 item (FI-40). Analisis statistik dengan metode chi-square untuk bivariat dan regresi logistik untuk multivariat, semua data disertai dengan interval kepercayaan 95%. *Hasil:* sindrom frailty didapatkan pada 25% (n=59) subyek penelitian, sedangkan pre-frail pada 72% (n=170) subyek dan sisanya tergolong fit. Metformin ditemukan mempunyai hubungan dengan sindrom frailty pada usila dengan diabetes mellitus tipe 2, yang tetap bermakna setelah dilakukan analisis multivariat (adjusted OR 0,043; IK 95% 0,019 – 0,099; p<0,001). *Kesimpulan:* metformin bersifat protektif terhadap kejadian sindrom frailty pada usila dengan diabetes melitus tipe 2.

Kata kunci: frailty, diabetes mellitus, metformin, usia lanjut.

ABSTRACT

Aim: to explore the possibility of metformin protective effect on frailty syndrome. *Methods:* this was a case control study conducted in subjects' ≥60 years old who visited the Geriatrics and Diabetes outpatient clinic of Cipto Mangunkusumo National Referral Hospital between March and June 2013. Diagnosis of frailty was established using the FI-40 item criteria. Statistical analysis was done with chi-square method for bivariate and logistic regression method in multivariate analysis, all data was accompanied with 95% confidence interval. *Results:* frailty syndrome was found in 25% of subjects (n=59), with median age of 72 years old (SD 6.27) and median of FI-40 item score was 0.18 (SD 0.085). Metformin was found to have a significant relationship with frailty syndrome in the elderly diabetics, which retained significant value after multivariate analysis (adjusted OR 0.043; 95% CI 0.019-0.099; p<0.001). *Conclusion:* metformin was shown to have protective effect against frailty syndrome in elderly diabetics.

Key words: frailty, diabetes mellitus, metformin, elderly.

INTRODUCTION

Frailty, a syndrome that was caused by dysfunctional aging and considered as a transitional state between autonomy and complete dependency, now widely linked with type 2 diabetes mellitus (T2DM).[1] Several clinical studies had shown that, insulin resistance and T2DM had been proven to raise the risk of frailty on the elderly. Furthermore, insulin resistance and prandial glucose level disturbances had been linked to one of the important component of frailty, which is sarcopenia. Obesity, which tightly linked to insulin resistance and T2DM, also linked to a state of sarcopenia which known as sarcopenic obesity.[2-6]

Oral anti-diabetic metformin has been linked with the inhibition of aging process through many laboratory studies. Studies from animal experiments, especially fruit flies and nematodes, had shown that metformin could prolong the species' life span around 40 to 200%.[7-10] Furthermore, population studies conducted in diabetics had also shown that metformin was able to prevent macro-vascular comorbid, which was linked with accelerated aging.[11] However, there was no direct data to show the effect of metformin to modulate elderly diabetics' functional status and frailty syndrome's risk.[7-9]

We conducted this study to explore the association between metformin use and the risk of frailty syndrome in diabetic elderly. We aimed to provide a scientific basis for further interventional studies on frail Indonesian elderly with metformin.

METHODS

The study was conducted with a case-control design and applied to the patients of the Geriatric and Diabetes Outpatient Clinic of Cipto Mangunkusumo National Referral Hospital (RSCM), aged 60 years old or older. The recruitment was done between March-June 2013; data acquisition was gathered by questionnaire and direct measurement of anthropometric and functional status variables. Study samples are patients who fulfilled the inclusion/exclusion criteria, and then categorized as: case (frail individuals according to FI-40 item criteria[12] (*see online appendix: www.inaactamedica.org/archives/2014/appendix/sumantri_vol.46-p.183.pdf*) and control (non frail individuals, randomly selected from the same catchment area as case). We excluded patients with: 1) Severe renal impairment (creatinine >2.0 g/dL and/or CCT <30 ml/min); 2) Liver cirrhosis; 3) Severe cardiac impairment (NYHA functional class III/IV) and 4) Severe lung impairment (COPD GOLD stage III/IV).

Bivariate analysis with chi square method was used to determine the relation between metformin use and frailty risk. Multivariate analysis with logistic regression was done to explore the influence of variables such as gender, age group, body mass index, diabetes control and length, and also comorbid such as chronic kidney disease stage I-III, COPD GOLD I-II, chronic liver disease and also chronic heart failure NYHA I-II.

This research was done with respect to patient's autonomy and integrity; it fulfills the ethical principles of the Helsinki Declaration and has ethical clearance from the Research Ethical Committee of University of Indonesia Faculty of Medicine (no. 250/H2FI/ETIK/2013).

RESULTS

We managed to recruite a total of 236 subjects (59 cases: 177 controls) from the estimated minimal sample size of 212 subjects (53 cases: 159 controls). Most of the subjects is female (57.6%; n=136), aged between 60-69 years old (50%; n=118); and with a median age of 69.5 years old (range 60-87 years; SD 6.24 years). The body mass index (BMI) showed a median of 24.4 (range 15.2-41.3; SD 4.08) and diabetes length of median 13 years (range 2-38 years; SD 8.043).

Metformin use showed a percentage of 73.7% (n=175) among the subjects, which 45.3% (n=107) of them use it since the diagnosis of diabetes and 15.3% (n=36) never used it at all. The length of metformin use showed a median 12 years (range 1-33 years; SD 7.69).

Frailty syndrome, with Frailty Index 40 item (FI-40) criteria, was found in 25% (n=59) of subjects, with pre-frail on 72% (n=170) subjects and the rest is fit/robust. The median score of FI-40 was 0.18 (range 0.05-0.475; SD 0.085),

Table 1. Study subject's characteristics according to frailty status

Parameter	Study group	
	Frail (%/n) n=59	Non-frail (%/n) n=177
Age group (%/n)		
- 60-69 years	35,6 / 21	54,8 / 97
- 70-79 years	47,5 / 28	39,5 / 70
- 80 years or older	16,9 / 10	5,6 / 10
BMI class (%/n)		
- Underweight	7,3 / 4	5,3 / 9
- Normal weight	29,1 / 16	25,3 / 43
- Overweight-Obese	63,6 / 35	69,4 / 118
Diabetes length (%/n)		
- <5 years	5,1 / 3	9,6 / 17
- 5-10 years	13,6 / 8	24,3 / 43
- >10 years	81,4 / 48	66,1 / 117
Diabetes control (%/n)*		
- Good	32,2 / 19	32,8 / 58
- Moderate	39 / 23	35 / 62
- Bad	28,8 / 17	32,2 / 57
Number of comorbid CIRS (%/n)**		
- High (score ≥10)	94,9 / 56	58,8 / 104
- Low (score <10)	5,1 / 3	41,2 / 73
Comorbid (% positive/n)		
- Cardiac	49,2 / 29	26,6 / 47
- Respiratory	20,3 / 12	5,1 / 9
- Kidney	66,1 / 39	41,2 / 73
- Hepatic	6,8 / 4	2,8 / 5

* Good (A1C<7, GDP <100, GD2PP <140) Moderate (A1C 7-8, GDP <126, GD2PP <200) Bad (A1C >8, GDP >140, GD2PP >200);
** CIRS = Cumulative Illness Rating Scale

with the median for frail group is 0.3 (range 0.25-0.475; SD 0.061) and non-frail 0.16 (range 0.05-0.244; SD 0.044). The subject's characteristic is described in **Table 1**.

Analysis on the Relationship between Metformin and Frailty

Chi square analysis on the risk of frailty in metformin users and non-users, showed a difference in frailty risk (OR 0.039; 95% CI 0.018-0.083; p<0.001). Then we conducted multivariate analysis by entering the agreed variables that fulfilled the requirements (p<0.25) into logistic regression. The variables that meet the requirements are age ≥80 year's old, length of T2DM, and also kidney, respiratory, hepatic and cardiac comorbid. The analysis showed

the risk of frailty between metformin users and non-users is 0.043 (adjusted OR; 95% CI 0.019-0.099; p<0.001).

Sub-group analysis then conducted to compare individuals that already received diabetes' therapy for 10 years or more. Individuals with metformin use since diagnosis (n=107) compared to metformin naive individuals (n=36) showed difference in terms of FI 40 score (0.17 vs. 0.30; 95% CI 0.16-0.18 vs. 0.27-0.33; p<0.001), number of comorbid (CIRS score 10.91 vs. 14.77; 95% CI 10.37-11.46 vs. 13.70-15.85; p<0.001) and current kidney function (eGFR 58.92 vs. 47.6 ml/min; 95% CI 54.70-63.14 vs. 42.30-53.08; p=0.004). Furthermore, metformin users showed difference in muscle

strength (handheld dynamometer 17.75 kg vs. 14.91 kg; 95% CI 16.51-18.99 vs.12.64-17.18; p=0.046) and body balance (functional reach test 26.07 cm vs. 20.65 cm; 95% CI 24.68-27.47 vs. 16.72-24.59; p=0.011).

DISCUSSION

The median score of FI-40 item in this study's subjects is 0.18 (range 0.05-0.475; SD 0.085), which is higher than mean FI-40 item score on Song et al's study (0.138±0.11).[13] This is mainly because a difference in study population, where in this study we recruited the subjects from outpatient rather than general population like study of song, diabetes and its accompanying comorbid was a vital component of frailty diagnosis using FI-40 item criteria, hence the difference could be predicted before.

Relationship of Metformin and Frailty syndrome

Bivariate analysis in our study had shown that individuals with metformin use had lower frailty risk compared to non-users. This 96.1% (OR 0.039) risk reduction showed metformin's ability to prevent deficit accumulation that could cause frailty. Multivariate analysis also showed that metformin is independently linked with the risk of frailty syndrome in elderly diabetics (adjusted OR 0.043). Further sub-group analysis showed lower comorbidities in individuals who used metformin since the start of diabetes diagnosis (CIRS score 10.91 vs. 14.77) compared to the metformin naive. The estimated glomerular filtration rate (eGFR), as a measure of kidney function, also showed a higher value in individuals that used metformin from the start (eGFR 58.92 vs. 47.6 ml/min).

Large population study (>50.000 subjects) conducted in Sweden, showed that metformin is able to lower the incidence of cardiovascular comorbid and mortality risk better than other anti-diabetics (2-13% reduction compared to sulfonylureas and 18-35% to insulin).[14] Our study showed that individuals with frailty had more comorbid; and metformin use from the start of diabetes diagnosis may have the ability to prevent that accumulation. Metformin's ability to prevent cardiovascular complications and frailty,

thought to result from its influence on the cellular aging process. Aging in diabetics happened in a much faster process than non-diabetics, this was in part caused by oxidative stress and the accumulation of advanced glycosylation end products (AGEs), which caused chronic inflammation and accelerated cellular damage and aging.[2,15-19] Metformin in animal studies and new onset diabetics has shown able to restore the natural body's antioxidant status, lower AGEs and inflammatory mediators' level, which usually increases in diabetics.[8,20-23]

This study also showed that one of the reason of metformin's ability in reducing frailty risk in the elderly is because its effect on muscle strength and balance. Metformin users in this study showed better muscle strength (handheld dynamometer 17.75 kg vs. 14.91 kg) and body balance (functional reach test 26.07 cm vs. 20.65 cm). Metformin's ability in improving muscle strength and balance is thought to result from its effect on peripheral insulin sensitivity. Studies had shown that metformin is able to improve peripheral muscle glucose uptake through its AMPK regulatory effect.[23,24] Furthermore, a study that was conducted on acute catabolic state reveals that, the use of metformin could improve the patients' ability to synthesize muscular protein.[25] Frailty syndrome itself has been proven to be a chronic inflammatory state linked with insulin resistance and muscle protein catabolism.[4-6,26-29]

Until recently, there is no study that linked the use of metformin with frailty syndrome on elderly diabetics. Furthermore, studies that linked metformin with aging process had not directly explored its effects on human. However, animal studies had shown metformin's ability to improve life span and decrease cancer incidence significantly.[8] Furthermore, observational studies on human had shown the link between metformin use and a decreasing incidence of several types of cancer in diabetics.[9,30-35] Metformin's ability to significantly decrease cancer incidence is very important, because carcinogenesis is considered as one of the consequences of accelerated and dysfunctional aging.[31,35-37]

Metformin was also considered to regulate aging with the same mechanism as caloric

restrictions through its effect on AMPK regulation.[8] Studies on caloric restriction on several human cultures, the most famous among them is the Okinawa Study, had shown that, individuals with lower caloric consumption had increased life span.[38] This Okinawa Study's result has been corroborated by experimental animal studies on the effect of caloric restrictions, on the life span of several species of mammals and primates.[8,39-41]

Limitations of This Study

Due to case control design used, we could not exactly draw conclusion on the temporality between metformin use and frailty incidence. We also could not predict the relationship between metformin dose and the severity of frailty syndrome. This may in turn distort the picture of frailty that is presented in this study.

CONCLUSION

Metformin had a protective effect on the risk of frailty syndrome in elderly diabetics. It is independently linked with frailty in elderly diabetics.

ACKNOWLEDGMENTS

REFERENCES

1. Bourdel-Marchasson I, Berrut G. Caring the elderly diabetic patient with respect to concepts of successful aging and frailty. Diabetes Metab. 2005;31(2):5S13-5S19.

2. Hubbard RE, Andrew MK, Fallah N, Rockwood K. Comparison of the prognostic importance of diagnosed diabetes, co-morbidity and frailty in older people. Diabet Med. 2010;27(5):603-6.

3. Cacciatore F, Testa G, Galizia G, et al. Clinical frailty and long-term mortality in elderly subjects with diabetes. Acta Diabetol 2012.

4. Kalyani RR, Varadhan R, Weiss CO, Fried LP, Cappola AR. Frailty status and altered glucose-insulin dynamics. J Gerontol A Biol Sci Med Sci 2012;67(12):1300-6.

5. Barzilay JI, Blaum C, Moore T, et al. Insulin resistance and inflammation as precursors of frailty: the cardiovascular health study. Arch Intern Med. 2007;167(7):635-41.

6. Kuo CK, Lin LY, Yu YH, Wu KH, Kuo HK. Inverse association between insulin resistance and gait speed in nondiabetic older men: results from the U.S. National Health and Nutrition Examination Survey (NHANES) 1999-2002. BMC Geriatr. 2009;9:49.

7. Anisimov VN, Berstein LM, Egormin PA, et al. Metformin slows down aging and extends life span of female SHR mice. Cell Cycle. 2008;7(17):2769-73.

8. Onken B, Driscoll M. Metformin induces a dietary restriction-like state and the oxidative stress response to extend C. elegans Healthspan via AMPK, LKB1, and SKN-1. PLoS One. 2010;5(1):e8758.

9. Anisimov VN. Metformin for aging and cancer prevention. Aging (Albany NY). 2010;2(11):760-74.

10. Mouchiroud L, Molin L, Dalliere N, Solari F. Life span extension by resveratrol, rapamycin, and metformin: The promise of dietary restriction mimetics for an healthy aging. Biofactors. 2010;36(5):377-82.

11. Capion N, Boye M, Ekstrom CT, Jensen TK. Infection dynamics of digital dermatitis in first-lactation Holstein cows in an infected herd. J Dairy Sci 2012;95(11):6457-64.

12. Mitnitski AB, Song X, Rockwood K. The estimation of relative fitness and frailty in community-dwelling older adults using self-report data. J Gerontol A Biol Sci Med Sci. 2004;59(6):M627-32.

13. Song X, Mitnitski A, Rockwood K. Prevalence and 10-year outcomes of frailty in older adults in relation to deficit accumulation. J Am Geriatr Soc. 2010;58(4):681-7.

14. Ekstrom N, Schioler L, Svensson AM, et al. Effectiveness and safety of metformin in 51 675 patients with type 2 diabetes and different levels of renal function: a cohort study from the Swedish National Diabetes Register. BMJ Open. 2012;2(4).

15. Singh T, Newman AB. Inflammatory markers in population studies of aging. Ageing Res Rev. 2011;10(3):319-29.

16. Poehls J, Wassel CL, Harris TB, et al. Association of adiponectin with mortality in older adults: the health, aging, and body composition study. Diabetologia. 2009;52(4):591-5.

17. Lu FP, Lin KP, Kuo HK. Diabetes and the risk of multi-system aging phenotypes: a systematic review and meta-analysis. PLoS One. 2009;4(1):e4144.

18. Figaro MK, Kritchevsky SB, Resnick HE, et al. Diabetes, inflammation, and functional decline in older adults: findings from the health, aging and body composition (ABC) study. Diab Care. 2006;29(9):2039-45.

19. Newman AB, Arnold AM, Naydeck BL, et al. "Successful aging": effect of subclinical cardiovascular disease. Arch Intern Med. 2003;163(19):2315-22.

20. Esteghamati A, Eskandari D, Mirmiranpour H, et al. Effects of metformin on markers of oxidative stress and antioxidant reserve in patients with newly diagnosed

type 2 diabetes: a randomized clinical trial. Clin Nutr. 2013;32(2):179-85.

21. Chakraborty A, Chowdhury S, Bhattacharyya M. Effect of metformin on oxidative stress, nitrosative stress and inflammatory biomarkers in type 2 diabetes patients. Diab Res Clin Pract 2011;93(1):56-62.

22. Tanaka Y, Uchino H, Shimizu T, et al. Effect of metformin on advanced glycation endproduct formation and peripheral nerve function in streptozotocin-induced diabetic rats. Eur J Pharmacol. 1999;376(1-2):17-22.

23. Nagi DK, Yudkin JS. Effects of metformin on insulin resistance, risk factors for cardiovascular disease, and plasminogen activator inhibitor in NIDDM subjects. A study of two ethnic groups. Diab Care. 1993;16(4):621-9.

24. Stumvoll M, Nurjhan N, Perriello G, Dailey G, Gerich JE. Metabolic effects of metformin in non-insulin-dependent diabetes mellitus. N Engl J Med. 1995;333(9):550-4.

25. Gore DC, Wolf SE, Sanford A, Herndon DN, Wolfe RR. Influence of metformin on glucose intolerance and muscle catabolism following severe burn injury. Ann Surg. 2005;241(2):334-42.

26. Ferrucci L, Harris TB, Guralnik JM, et al. Serum IL-6 level and the development of disability in older persons. J Am Geriatr Soc 1999;47(6):639-46.

27. Penninx BW, Kritchevsky SB, Newman AB, et al. Inflammatory markers and incident mobility limitation in the elderly. J Am Geriatr Soc. 2004;52(7):1105-13.

28. Rasmussen BB, Fujita S, Wolfe RR, Mittendorfer B, Roy M, Rowe VL, et al. Insulin resistance of muscle protein metabolism in aging. FASEB J. 2006;20(6):768-9.

29. 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(5):e10805.

30. Giovannucci E, Harlan DM, Archer MC, et al. Diabetes and cancer: a consensus report. CA Cancer J Clin. 2010;60(4):207-21.

31. Luo Z, Zang M, Guo W. AMPK as a metabolic tumor suppressor: control of metabolism and cell growth. Future Oncol. 2010;6(3):457-70.

32. Vigneri P, Frasca F, Sciacca L, Pandini G, Vigneri R. Diabetes and cancer. Endocr Relat Cancer. 2009;16(4):1103-23.

33. Vazquez-Martin A, Oliveras-Ferraros C, Lopez-Bonet E, Menendez JA. AMPK: Evidence for an energy-sensing cytokinetic tumor suppressor. Cell Cycle. 2009;8(22):3679-83.

34. Berstein LM. Metformin, insulin, breast cancer and more. Future Oncol. 2009;5(3):309-12.

35. Vazquez-Martin A, Oliveras-Ferraros C, Cufi S, Martin-Castillo B, Menendez JA. Metformin and energy metabolism in breast cancer: from insulin physiology to tumour-initiating stem cells. Curr Mol Med. 2010;10(7):674-91.

36. Motoshima H, Goldstein BJ, Igata M, Araki E. AMPK and cell proliferation--AMPK as a therapeutic target for atherosclerosis and cancer. J Physiol. 2006;574(Pt 1):63-71.

37. Green AS, Chapuis N, Lacombe C, Mayeux P, Bouscary D, Tamburini J. LKB1/AMPK/mTOR signaling pathway in hematological malignancies: From metabolism to cancer cell biology. Cell Cycle. 2011;10(13).

38. Kagawa Y. Impact of Westernization on the nutrition of Japanese: changes in physique, cancer, longevity and centenarians. Prev Med. 1978;7(2):205-17.

39. Colman RJ, Anderson RM, Johnson SC, et al. Caloric restriction delays disease onset and mortality in rhesus monkeys. Science. 2009;325(5937):201-4.

40. Huffman DM, Moellering DR, Grizzle WE, Stockard CR, Johnson MS, Nagy TR. Effect of exercise and calorie restriction on biomarkers of aging in mice. Am J Physiol Regul Integr Comp Physiol. 2008;294(5):R1618-27.

41. Weindruch R. The retardation of aging by caloric restriction: studies in rodents and primates. Toxicol Pathol. 1996;24(6):742-5.