Effects of low-dose metformin on pre-frailty among middle-aged and elderly pre-diabetic people

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Abstract

Background Pre-frailty has been identified as a clinically silent mechanism pre-disposing people to frailty. The goal of this study is to investigate the impact of low-dose metformin on pre-diabetic pre-frail patients (>50 years) on skeletal muscle mass, speed of gait, handgrip power, and health-related quality of life (HR-QoL).

Methods We did a retrospective cohort study of subjects aged 50 years and older who were diagnosed with pre-frailty (one or two criteria present based on Fried Frailty Index) and pre-diabetes (HbA1c 5.7% to 6.4%) from May 2018 to April 2020. Subjects taking low-dose metformin were compared with non-metformin participants through a review of the medical records. The results were analysed at baseline and 6–12 months post-prescription with or without metformin. All data were accompanied by a 95% confidence interval.

Results One hundred and thirteen pre-diabetic and pre-frail subjects were recruited to metformin [the mean metformin administration was 750 (140) mg/day] (n = 58) or control group (n = 55). The average age was 66.3 (6.8) years old, with 52.2% of the population being female. The baseline demographic, nutritional, physical, and mental status data did not differ between groups. In comparison with the control group, an 8.9 (1.8) month low-dose metformin intervention resulted in a higher skeletal muscle mass index of 1.26 (1.66) kg/m2 (P = 0.029), a faster gait speed of 0.15 (0.22) m/s (P = 0.011), and a greater handgrip strength of 2.1 (2.9) kg (P = 0.037). However, there was no difference in myostatin serum levels or HR-QoL between groups.

Conclusions Low-dose metformin was statistically and clinically meaningful to improve the original skeletal muscle mass index, gait speed, and grip strength as part of the sarcopenia dimension, but the Euro Quality of Life-5 Dimensions index and myostatin serum levels did not change significantly.

Keywords Insulin resistance; Metformin; Myostatin; Pre-diabetes; Pre-frailty; Sarcopenia

Sarcopenia leads to the development of the condition of frailty. In older people, sarcopenia is a loss of muscle strength and mass and is a significant determinant of the probability of declining and diminished capacity to perform everyday living tasks, often leading to disability, loss of independence, and death. The effect of sarcopenia on elderly morbidity, mortality, and health care expenditures seems to be a major subject of discussion in science and public policy.¹ Sarcopenia is thought to be linked to myostatin, a transforming growth factor-β that causes muscle protein degradation leading to inhibition of muscle growth.²,³

Frailty syndrome means a continuous continuum of normal/solid, pre-frail, frail, and dynamically shifting states from stable to frail and backward. Frailty is characterized by the model proposed by Fried as the existence of at least three of five physical indicators: slowness (reduced speed of gait), weakness (reduced strength of grip), low physical activity, weight loss, and exhaustion. Individuals with one or two
markers are classified as pre-frail. The prevalence of pre-frailty at the community level ranges from 13.4% to 71.6% depending on the geographic region and the screening procedures used, and the prevalence of frailty is commonly believed to be 3.9% and 51.4%.4,5 The incidence of a frailty disorder is strongly linked to inflammation, insulin resistance, diabetes mellitus (DM), low vitamin D and protein intake, polypharmacy (≥5 prescribed drugs), and depression.6–10

Administration of metformin potentially improves frailty syndrome by modifying insulin resistance, hyperglycaemia, inflammation, and myostatin levels. Metformin not only activates cellular metabolic adenosine monophosphate-activated protein kinase (AMPK) but also inhibits nuclear factor-kb and mechanistic target of rapamycin.11–13 Metformin also improves the activity of Na\(^+\)K\(^+\)ATPase and increases the circulation of nitric oxide that optimizes cellular energy production. Previous studies, on the other hand, have shown that AMPK can trigger muscle protein degradation and muscle protein synthesis down-regulation by stimulating myostatin expression and mechanistic target of rapamycin signal.14,15 A case-control study indicated the protective effect of metformin against frailty syndrome.16 The study showed a significant difference in frailty status between metformin-treated and non-metformin-treated patients with type 2 DM. However, the effect of low-dose metformin on pre-frailty, in particular on the physical components of sarcopenia and serum myostatin, has not been investigated.

Therefore, we aimed to explore the effects of low-dose metformin on handgrip capacity, gait velocity, serum level of myostatin, and health-related quality of life (HR-QoL) among pre-frail-status pre-diabetic subjects.

### Patients and methods

A retrospective cohort study was carried out by analysing the medical history of residents with pre-diabetes and pre-frailty who were routinely assessed and reported every 6 months during their retirement stay.

Data extracted from residents aged 50 years and older with pre-frail (one or two criteria present based on Fried Frailty assessment full form score plus food record of two weekdays and one holiday), and body composition (Bioelectrical Impedance Analysis Tanita BC 420 MA).18 Manual grip strength was measured and expressed in kilogrammes of force using a digital dynamometer (Jamar\(^\circledast\) Dynamometer, Patterson Medical, IL, USA) and carried out under the prescribed protocol of the American Society of Hand Therapists (ASHT). The 6 m walking test was performed to measure the usual speed of the gait. HR-Qol was assessed using the Euro Quality of Life-5 Dimensions (EQ-5D) questionnaire with a simplified 5-point Likert scale.15 Also, serum myostatin, oral glucose tolerance, as well as liver and kidney function tests were included in the blood test every 6 months. The serum level of myostatin was measured using the ELISA kit Cat. No. KT-22930.

The research was conducted with respect to patient autonomy and integrity; it complies with the ethical principles of the Helsinki Declaration and has ethical clearance from the Institutional Review Boards.

### Statistical analysis

A sample size of 55 per group is needed to compare differences in the Frailty Index 40 item score between subjects treated with or without low-dose metformin (based on the findings of Sumantri et al.), with power of 0.80 and α of 0.05.16 Using Student’s independent t-test and one-way analysis of variance for continuous data and \(\chi^2\) test for bivariate and logistic regression method in multivariate analysis, discrepancies between groups were compared, and all data were accompanied by a 95% confidence interval (CI). Statistical analysis was carried out using GraphPad Prism Version 6 (GraphPad Software, La Jolla, CA, USA) and IBM SPSS Version 23 (IBM, Armonk, NY, USA). A P value of <0.05 was statistically significant.

### Results

One hundred and thirteen pre-diabetic and pre-frail subjects were recruited to metformin [the mean metformin adminis-
tration was 750 (140) mg/day for 8.9 (1.8) months] (n = 58) or control group (n = 55). The mean age was 66.3 (6.8) years old, and 52.2% were female participants. Based on Asian Working Group of Sarcopenia criteria, there were no subjects with sarcopenia. Metformin users were less likely to take calcium and vitamin D supplements and more likely to consume acetylsalicylic acid. Except for medication use, there was no difference in baseline demographic and nutritional status data between groups (P > 0.05) (Tables 1 and 2).

There was also no difference in groups in terms of baseline physical and mental health (P > 0.05) (Table 3). Table 3 indicates that the baseline walking speed of 0.96 (0.24) m/s in the metformin group, while the mean usual walking speed of 0.94 (0.23) m/s in the control group. In the metformin group, the baseline median handgrip strength was 26 (12–40) kg, while in the control group, 25 (14–35) kg. In all subjects, the baseline median serum level of myostatin was 31.26 (13.77–83.15) ng/mL. The baseline median EQ-5D index score for the metformin group was 0.77 (0.57–1.0) with an EQ-5D VAS score of 70 (40–90), while in the control group, the median EQ-5D index score was 0.79 (0.62–1.0) with an EQ-5D VAS score of 75 (45–100). Both groups had a high compliance rate, which was 90.25% (5.67) in the metformin group and 92.55% (5.96) in the control group.

The analysis of variance statistical test showed that there was a substantial difference in normal gait velocity between the metformin and control group at the end of the intervention, which remained statistically significant even after adjustment for age, sex, calcium-vitamin D or acetylsalicylic acid intake, and baseline grip strength, calf circumference, and BMI (Table 4). There was a noticeable increase in the usual gait speed in the metformin group. In the unadjusted model, there was also a significant difference in BMI, waist circumference, handgrip intensity, and skeletal muscle mass index between the metformin and control groups, with a statistically significant difference after adjusting for potential prognostic factors. However, there was no substantial difference in myostatin serum level and HR-QoL between the two groups (Table 4). The dietary intake, as well as the physical activity levels of metformin and control group, were similar until the end of the intervention (data not shown). Gastrointestinal symptoms such as diarrhoea, nausea, bloating, and epigastric pain were the side effects of metformin commonly reported in this study. However, the incidence of serious adverse events was similar between groups. Besides, lactic acidosis has not been observed in either group.

### Discussion

The mean gait velocity in the metformin group at the end of the procedure represented a mean increase of 0.15 (0.22) m/s in gait velocity. This result is consistent with the cohort study, which stated that the reduction in gait rate was not only lesser in diabetic patients receiving insulin-sensitizing medicines (metformin or thiazolidinedione) than in diabetic patients receiving other forms of oral antidiabetic medicines, but also lesser than non-diabetic patients.20

Previous studies have found that the minimum increase in gait velocity by 0.05 m/s is considered to be significant, while a marked improvement in gait velocity is considered to be 0.10 m/s.21,22 The age-adjusted relative risk ratio for B-ADL dependence per 0.1 m/s higher velocity was 0.68 (95% CI 0.57–0.81) for male participants and 0.74 (95% CI 0.66–0.82) for female participants.23 Every 0.1 m/s decrease in gait speed was also associated with a 7% increase in the risk of falling.24,25 A meta-analysis of nine cohorts concluded that gait speed was associated with pooled hazard ratio 0.88 (95% CI 0.87–0.90) per 0.1 m/s improvement.26 Consequently, not just statistically important but also clinically relevant was the 0.15 (0.22) m/s increase in the usual gait speed observed in our research.

The condition of insulin resistance reduces muscle mass and muscle contractility due to cytokine, increased myostatin expressions, and ineffective activity of insulin, resulting in decreased blood flow and glucose utilization of the skeletal muscle, as well as degradation of muscle protein.27–29 Every one increase in the homeostasis model assessment of insulin resistance standard deviation in non-diabetic elderly patients was parallel to a gait velocity reduction of

### Table 1 The demographic baseline of the subjects

| Characteristics                  | Metformin (n = 58) | Control (n = 55) |
|----------------------------------|--------------------|-----------------|
| Age (years), median (min–max)    | 66.7 (6.1)         | 65.9 (7.6)      |
| Sex, n (%)                       |                    |                 |
| Female                           | 31 (53.4)          | 28 (50.9)       |
| Male                             | 27 (46.6)          | 27 (49.1)       |
| Level of education, n (%)        |                    |                 |
| Low                              | 8 (13.8)           | 5 (9.1)         |
| Moderate                         | 17 (29.3)          | 21 (38.3)       |
| High                             | 33 (56.9)          | 29 (52.7)       |
| Comorbidities, n (%)             |                    |                 |
| Hypertension                     | 45 (78.4)          | 44 (79.3)       |
| Hyperlipidaemia                  | 38 (65.8)          | 34 (62.1)       |
| Degenerative joint disease       | 25 (43.5)          | 24 (43.5)       |
| Coronary heart disease           | 11 (19.5)          | 11 (20.9)       |
| CIRS score, n (%)                |                    |                 |
| ≤5                               | 20 (34.5)          | 18 (32.7)       |
| >5                               | 38 (65.5)          | 37 (67.3)       |
| Polypharmacy, n (%)              |                    |                 |
| Yes                              | 38 (65.5)          | 31 (56.4)       |
| No                               | 20 (34.5)          | 24 (43.6)       |
| Medications used, n (%)          |                    |                 |
| Statin                           | 36 (62.1)          | 42 (76.4)       |
| Angiotensin receptor blocker (ARB)| 28 (48.3)         | 24 (43.6)       |
| ACE inhibitor                    | 5 (8.6)            | 7 (12.7)        |
| Calcium-vitamin D supplement     | 9 (15.5)           | 16 (29.1)       |
| Acetylsalicylic acid             | 24 (41.4)          | 13 (23.6)       |
| Proton pump inhibitor (PPI)      | 25 (43.1)          | 31 (64.6)       |

ACE, angiotensin converting enzyme; CIRS, cumulative illness rating scale.
0.04 m/s. Improvement in insulin resistance, inflammation, oxidative stress, and nitric oxide status may be responsible for a significant gait speed improvement in the metformin group.27 Similarly, our research has shown that the substantial decrease in BMI and waist circumference among metformin group subjects may be associated with an improvement in the status of insulin resistance (Table 4).

Our study showed that handgrip strength was an appropriate parameter to investigate the effects of low-dose metformin. The purpose of handgrip strength measurement is to

### Table 2 Baseline features of nutritional status parameter of subjects

| Characteristics                          | Metformin (n = 58) | Control (n = 55) |
|------------------------------------------|--------------------|-----------------|
| **Anthropometry measurements, mean (SD)**|                    |                 |
| Mid-arm circumference (cm)               | 30.65 (3.3)        | 29.95 (2.93)    |
| Male                                     | 30.08 (2.98)       | 29.70 (3.09)    |
| Female                                   | 30.89 (3.06)       | 30.61 (2.78)    |
| Upper-arm muscle circumference (cm)      | 24.37 (2.33)       | 23.44 (1.98)    |
| Male                                     | 24.79 (2.54)       | 23.73 (1.70)    |
| Female                                   | 24.09 (2.15)       | 23.27 (2.67)    |
| Waist circumference (cm)                 | 88.44 (9.16)       | 87.35 (9.71)    |
| Male                                     | 89.23 (10.24)      | 88.02 (11.35)   |
| Female                                   | 88.39 (9.59)       | 87.05 (9.14)    |
| Thigh circumference (cm)                 | 51.88 (4.35)       | 48.95 (4.69)    |
| Male                                     | 50.44 (3.52)       | 46.46 (3.44)    |
| Female                                   | 52.00 (4.89)       | 49.97 (5.19)    |
| Calf circumference (cm)                  | 34.82 (4.25)       | 34.74 (3.98)    |
| Male                                     | 35.16 (3.78)       | 35.87 (3.67)    |
| Female                                   | 33.79 (3.51)       | 34.21 (3.83)    |
| BMI (kg/m²)                              | 25.40 (3.45)       | 24.90 (3.30)    |
| Male                                     | 24.17 (2.58)       | 23.91 (2.81)    |
| Female                                   | 26.37 (2.83)       | 25.90 (3.25)    |
| **Body composition**                     |                    |                 |
| Skeletal muscle mass (kg), median (min–max) | 28.8 (19.0–42.8)   | 28.4 (18.3–44.7) |
| Skeletal muscle mass index (kg/m²), median (min–max) | 11.53 (7.69–15.35) | 11.42 (7.50–15.16) |
| Male, mean (SD)                          | 12.29 (1.68)       | 12.11 (1.59)    |
| Female, mean (SD)                        | 9.79 (1.21)        | 9.85 (1.34)     |
| Fat mass (kg), mean (SD)                 | 19.92 (7.25)       | 18.63 (6.88)    |
| Male                                     | 16.52 (4.32)       | 16.16 (5.13)    |
| Female                                   | 20.99 (7.7)        | 20.26 (6.85)    |
| **Dietary intake**                       |                    |                 |
| Energy (Kcal), mean (SD)                 | 1384.60 (320.87)   | 1392.27 (305.32) |
| Protein (g), mean (SD)                   | 45.53 (11.80)      | 43.56 (12.29)   |
| Vitamin D (mcg), median (min–max)        | 4.1 (3.1–20.8)     | 3.8 (2.5–17.10) |
| Calcium (mg), median (min–max)           | 374.5 (66.3–2151.5) | 352.25 (79.7–1848.7) |
| OGTT, mean (SD)                          | 109.47 (9.26)      | 110.21 (9.85)   |
| Male                                     | 1256.21 (519.11)   | 1278.55 (535.71) |
| Female                                   | 12.39 (5.1)        | 12.28 (5.0)     |
| Post 75 g glucose load (mg/dL)           | 147.67 (30.48)     | 156.31 (33.68)  |

BMI, body mass index; OGTT, oral glucose tolerance test.

### Table 3 Baseline features of the physical and mental status levels of subjects

| Characteristics                          | Metformin (n = 58) | Control (n = 55) |
|------------------------------------------|--------------------|-----------------|
| B-ADL score, n (%)                       |                    |                 |
| Independence                             | 52 (89.7)          | 50 (90.9)       |
| Mild dependency                          | 6 (10.3)           | 5 (9.1)         |
| PASE score (Kcal per week), mean (SD)    | 1256.21 (519.11)   | 1278.55 (535.71) |
| Fl 40 items score, mean (SD)             | 0.149 (0.040)      | 0.150 (0.040)   |
| Handgrip strength (kg), med (min–max)    | 26 (12–40)         | 25 (14–35)      |
| Male, mean (SD)                          | 32.3 (5.65)        | 30.7 (5.00)     |
| Female, mean (SD)                        | 20.4 (3.83)        | 18.5 (3.72)     |
| Gait speed (m/s), mean (SD)              | 0.96 (0.24)        | 0.94 (0.23)     |
| Male                                     | 1.03 (0.25)        | 1.04 (0.23)     |
| Female                                   | 0.92 (0.24)        | 0.90 (0.26)     |
| Myostatin serum level (ng/mL), median (min–max) | 31.26 (13.77–83.15) | 34.83 (18.33–83.15) |
| Health-related quality of life: EQ-5D index score, median (min–max) | 0.77 (0.57–1.0)  | 0.79 (0.62–1.0) |
| Health-related quality of life: EQ-5D VAS Score, median (min–max) | 70 (40–90)        | 75 (45–100)     |
| Drug compliance (%), mean (SD)           | 90.25 (5.67)       | 92.55 (5.96)    |

B-ADL, Bayer-activities of daily living scale; EQ-5D, Euro Quality of Life-5 Dimensions; Fl, Frailty index; PASE, physical activity scale for the elderly; VAS, visual analogue scale.
evaluate the isometric hand muscle contraction that is a sudden, fast, and high force activity. The muscle fibres that are particularly involved in this type of activity are type II muscle fibre (fast twitch), the energy source of which is the anaerobic metabolism of ATP and creatine phosphate stored in the muscle. Metformin, which operates through AMPK, could promote mitochondrial fission to improve mitochondrial respiration and restore the mitochondrial life cycle. On the opposite, adenine nucleotides are decreased by supra-pharmacological metformin concentrations, resulting in mitochondrial respiration being halted. Recent studies have shown that metformin simulates sestrins that imitate the advantages of exercise by increasing anabolic signals and decreasing muscle catabolic signals.

The 6 m walking test is a dynamic, constant, and rhythmic muscle contraction without fatigue on the oxygen transport system. Energy sources for this form of activity can derive not only from the anaerobic metabolism of creatinine phosphate but also from the aerobic metabolism of glycogen and glucose. By enhancing the insulin-resistant condition, metformin administration improves the glucose and calcium uptake of the skeletal muscle. In the metformin group, therefore, gait velocity improvement occurred. However, further research is needed on the mechanism of how metformin improves the speed of the gait, particularly regarding the metabolism of muscle energy.

In this study, myostatin serum levels were higher because our subjects’ average and a higher proportion of body mass index were categorized as overweight-obese and all subjects were in a pre-diabetic condition. Furthermore, in type 2 DM subjects, messenger RNA (mRNA) myostatin expressions in the muscle were 1.4 times higher compared with normal subjects. However, at the end of the observation, our research did not find a significant difference in myostatin serum levels between the metformin and control groups. There was also no marked difference in the serum level of myostatin between subjects in the metformin group before and after the intervention. The impact of metformin on myostatin expression appears to be complex. Metformin boosted myostatin expression at low dosages but lowered myostatin expression and protein level at high quantities. Metformin may overactivate AMPK at high doses, reducing total protein synthesis and anabolic metabolism, including the production of myostatin. Furthermore, only myostatin mRNA expression in muscle can directly represent myostatin’s biological activity, and this study cannot verify if metformin affects myostatin mRNA expression in skeletal muscle.

The median EQ-5D index score in our sample was high because most subjects with a B-ADL score of 19–20 had good functional status and subjects with depression and cognitive disability were excluded from our research. Low-dose metformin administration showed no change in HR-QoL among middle-aged and older people with pre-diabetes. Metformin does not appear to have directly increased the overall HR-
QoL, but rather enhanced mobility, which is known to be one of several HR-QoL dimensions. Improving mobility is expected in the future to increase the ability of participants in everyday life activities.26

There were several limitations to this study. The body composition measurement used Bioelectrical Impedance Analysis in this study was not as accurate as dual-energy X-ray absorptiometry (DXA). Besides, the objective measurement of insulin resistance and inflammation mediators, as well as the measurement of lower extremity strength, were not observed in this study. Therefore, we cannot fully explain the mechanism of metformin to improve the outcome of the study. Furthermore, there was certainly no muscle biopsy to evaluate myostatin mRNA expression in this study. It remains undetermined, therefore, whether metformin has affected the expression of myostatin in the skeletal muscle.

Our study indicated that low-dose metformin administration to middle-aged and elderly subjects with pre-diabetes and pre-frailty was statistically and clinically effective in improving gait speed, grip strength, and skeletal muscle mass index, but did not directly reduce myostatin serum levels and further improve health-related quality of life.

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Conflict of interest

None declared.

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References

1. Dhillon RJ, Hasni S. Pathogenesis and management of sarcopenia. Clin Geriatr Med 2017;33:17–26.
2. White TA, LeBrasseur NK. Myostatin and sarcopenia: opportunities and challenges—a mini-review. Gerontology 2014;60:289–293.
3. Huang Z, Chen X, Chen D. Myostatin: a novel insight into its role in metabolism, signal pathways, and expression regulation. Cell Signal 2011;23:1441–1446.
4. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001;56:M146–M156.
5. Siriwathana DD, Hardoon S, Rait G, Weerasinghe MC, Walters KR. Prevalence of frailty and prefrailty among community-dwelling older adults in low-income and middle-income countries: a systematic review and meta-analysis. BMJ Open 2018;8:e018195.
6. Allalou J, Karunanithan S, Eisenberg MJ, Alexander KP, Bergman H. Role of frailty in patients with cardiovascular disease. Am J Cardiol 2009;103:1616–1621.
7. Ensrud KE, Ewing SK, Fredman L, Hochberg MC, Cauley JA, Hillier TA, et al. Circulating 25-hydroxyvitamin D levels and frailty status in older women. J Clin Endocrinol Metab 2010;95:5266–5273.
8. Schoufour JD, Franco OH, Kiefte-de Jong JC, Trajanoska K, Stricker B, Brusselle G, et al. The association between dietary protein intake, energy intake and physical frailty: results from the Rotterdam Study. Br J Nutr 2019;121:393–401.
9. Gnjidic D, Hilmer SN, Blyth FM, Naganathan V, Waite L, Seibel MJ, et al. Polypharmacy cutoff and outcomes: five or more medicines were used to identify community-dwelling older men at risk of different adverse outcomes. J Clin Epidemiol 2012;65:989–995.
10. Lin HC, Chang SF, Chen YH. The relations among physical indicators, cognitive status, community participation, and depression of the frail male elderly in Taiwan. Am J Mens Health 2020;14:1557988320974462.
11. Graham GG, Punt J, Arora M, Day RO, Dongue MP, Duong J, et al. Clinical pharmacokinetics of metformin. Clin Pharmacokinet 2011;50:81–98.
12. Salminen A, Hyttinen JM, Kaamiranta K. AMP-activated protein kinase inhibits NF-κB signaling and inflammation: impact on healthspan and lifespan. J Mol Med (Berl) 2011;89:667–676.
13. Iosida K, Young JL, Zirlk A, MacFarlane LA, Tsuboi N, Gerdes N, et al. Metformin inhibits proinflammatory responses and nuclear factor-kappaB in human vascular wall cells. Artheroscler Thromb Vasc Biol 2006;26:611–617.
14. Deng Z, Luo P, Lai W, Song T, Peng J, Wei HK. Myostatin inhibits eEF2K-eEF2 by regulating AMPK to suppress protein synthesis. Biochem Biophys Res Commun 2017;494:278–284.
15. Thomson DM. The role of AMPK in the regulation of skeletal muscle size, hypertrophy, and regeneration. Int J Mol Sci 2018;19:3125.
16. Sumantri S, Setiati S, Purnamasari D, Dewiasty E. Relationship between metformin and frailty syndrome in elderly people with type 2 diabetes. Acta Med Indones 2014;46:183–188.
17. Buysschaert M, Medina JL, Buysschaert B, Bergman M. Definitions (and current controversies) of diabetes and prediabetes. Curr Diabetes Rev 2016;12:8–13.
18. Chen LK, Liu LK, Woo J, Assantachai P, Auyeung TW, Bahyah KS, et al. Sarcopenia in Asia: consensus report of the Asian Working Group for Sarcopenia. J Am Med Dir Assoc 2014;15:95–101.
19. Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. Ann Med 2001;33:337–343.
20. Lee CG, Schwartz AV, Yaffe K, Hillier TA, LeBlanc ES, Cawthon PM, et al. Changes in physical performance in older women according to presence and treatment of...
diabetes mellitus. J Am Geriatr Soc 2013; 61:1872–1878.
21. Perera S, Mody SH, Woodman RC, Studenski SA. Meaningful change and responsiveness in common physical performance measures in older adults. J Am Geriatr Soc 2006;54:743–749.
22. Peel NM, Kuys SS, Klein K. Gait speed as a measure in geriatric assessment in clinical settings: a systematic review. J Gerontol A Biol Sci Med Sci 2006;54:743–749.
23. Perera S, Patel KV, Rosano C, Rubin SM, Satterfield S, Harris T, et al. Gait speed predicts incident disability: a pooled analysis. J Gerontol A Biol Sci Med Sci 2016;71:63–71.
24. Kyrdalen IL, Thingstad P, Sandvik L, Ormstad H. Associations between gait speed and well-known fall risk factors among community-dwelling older adults. Physiother Res Int 2019;24:e1743.
25. Meyer K. Gait speed as a fall predictor for elderly patients in rehabilitation. PT Critically Appraised Topics 2010; Paper 20.
26. Studenski S, Perera S, Patel K, Rosano C, Faulkner K, Inzitari M, et al. Gait speed and survival in older adults. JAMA 2011;305:50–58.
27. 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.
28. Okoro CA, Zhong Y, Ford ES, Balluz LS, Strine TW, Mokdad AH. Association between the metabolic syndrome and its components and gait speed among U.S. adults aged 50 years and older: a cross-sectional analysis. BMC Public Health 2006;6:282.
29. Louis E, Raue U, Yang Y, Jemiolo B, Trappe S. Time course of proteolytic, cytokine, and myostatin gene expression after acute exercise in human skeletal muscle. J Appl Physiol 1985;2007:1744–1751.
30. Mäderová D, Krumpolec P, Slobodová L, Schön M, Tírpáková V, Kováníčová Z, et al. Acute and regular exercise distinctly modulate serum, plasma and skeletal muscle BDNF in the elderly. Neuropeptides 2019;78:101961.
31. Ziganshin AU, Khairullin AE, Teplov AY, Gabdrakhmanov AI, Ziganshina LE, Hoyle CH, et al. The effects of ATP on the contractions of rat and mouse fast skeletal muscle. Muscle Nerve 2019;59:509–516.
32. Wang Y, An H, Liu T, Qin C, Guo S, et al. The effects of ATP on the contractions of rat and mouse fast skeletal muscle. Muscle Nerve 2019;59:509–516.
33. Kirubel E, Samuel MS, Anjum MS, Aggarwal SS, Chanda S, et al. Metformin-induced ablation of microRNA 21-5p releases Sestrin-1 and CAB39L antitumoral activities. Cell Discov 2017;3:17022.
34. Segalès J, Perdigueru E, Serrano AL, Sousa-Victor P, Ortel L, Jardi M, et al. Sestrin prevents atrophy of disused and aging muscles by integrating anabolic and catabolic signals. Nat Commun 2020;11:189.
35. Davidoff F, Bertolini D, Haas D. Enhancement of the mitochondrial Ca2+ uptake rate by phenethylbiguanide and other organic cations with hypoglycemic activity. Diabotes 1978;27:757–765.
36. Amor M, Itariu BK, Moreno-Viedma V, Keindl M, Jürets A, Prager G, et al. Serum myostatin is upregulated in obesity and correlates with insulin resistance in humans. Exp Clin Endocrinol Diabetes 2019;127:550–556.
37. Brandt C, Nielsen AR, Fischer CP, Hansen J, Pedersen BK, Plomgaard P. Plasma and muscle myostatin in relation to type 2 diabetes. PLoS ONE 2012;7:e37236.
38. Das AK, Yang QY, Fu X, Liang JF, Duarte MS, Zhu MJ, et al. AMP-activated protein kinase stimulates myostatin expression in C2C12 cells. Biochem Biophys Res Commun 2012;427:36–40.
39. von Haehling S, Morley JE, Coats AJS, Anker SD. Ethical guidelines for publishing in the Journal of Cachexia, Sarcopenia and Muscle: update 2019. J Cachexia Sarcopenia Muscle 2019;10:1143–1145.