Improvement of physical activity significantly reduced serum hepatocyte growth factor levels in a general population: 10 year prospective study

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Received: 28 April 2022 / Accepted: 26 October 2022 / Published online: 9 November 2022 © Springer Japan KK, part of Springer Nature 2022

Abstract
Hepatocyte growth factor (HGF) is an adipocytokine elevated in obese subjects. We have previously reported that serum HGF levels were significantly associated with insulin resistance or components of the metabolic syndrome. However, it has been unknown how physical activity (PA) affects HGF levels after a long-term follow-up. Our aim was to clarify the association between PA changes and HGF levels as well as cerebro-cardiovascular disease (CVD) development, during a 10 year follow-up period in a Japanese general population. Of 1320 subjects who received a health check-up examination in Tanushimaru town in 1999, 903 subjects (341 males and 562 females), who received the examination both in 1999 and 2009 were enrolled. We evaluated their PA levels by Baecke questionnaire in 1999 and by a simple questionnaire in 2009. We measured the HGF levels by ELISA method in 1999 and 2009. We divided the subjects into four PA groups, stable low PA, increased PA, decreased PA, and stable high PA. Using these questionnaires, we compared their PA and HGF levels after an interval of 10 years. A significant inverse association was found between PA changes and HGF levels at 10 years, after adjustment for age and sex. The HGF levels of the increased PA group were significantly lower than stable low PA \((p = 0.038)\), and the increased PA group showed reduced CVD development compared to the stable low PA group after adjustment for age and sex \((p = 0.012)\). Our data demonstrated that improvement of PA levels was associated with reduced HGF levels and CVD development.

Keywords Physical activity · Hepatocyte growth factor · Epidemiology

Introduction
Hepatocyte growth factor (HGF), discovered in 1984 [1], was purified and isolated in 1986 [2]. We have previously reported that serum HGF levels were strongly associated with the metabolic syndrome [3] and the development of insulin resistance [4]. In a sense, serum HGF has been recognized as a marker of metabolic syndrome. On the other hand, regular physical activity (PA) can reduce weight and blood pressure, and also can improve lipid disorders, including elevating high density lipoprotein cholesterol (HDL-C) and lowering triglycerides [5, 6], which also improves the insulin resistance [7, 8]. However, the impact of PA on serum HGF levels is still unclear.

It is well-known that one of components of metabolic syndrome is large waist circumference but not obese per se. Our previous reports [3, 4] indicated that waist circumference, but not body mass index (BMI), affects serum HGF, suggesting the importance of fat distribution, i.e., abdominal obesity for high serum HGF. The pathophysiological mechanisms in the role of abdominal obesity for high HGF is the adipose tissue as an endocrine organ that secretes multiple growth factors and cytokines. Our previous [3] study in a relatively large number of subjects suggests a pathophysiological relationship between abdominal obesity and serum HGF levels. Higher PA may be inversely associated with abdominal obesity and may reduce metabolic syndrome risk.
Therefore, in the present study, we examined the relationship between changes of PA and serum HGF levels during 10 years follow-up. Moreover, we also examined that the effects of PA improvement on the serum HGF levels in a community-dwelling Japanese general population.

Materials and methods

Study population

A periodic epidemiologic survey was performed in 1999 and 2009 in a rural farming community located in south-western Japan (Tanushimaru town). Tanushimaru study was a Japanese cohort of the Seven Countries Study [9]. As previously reported, the demographic characteristics of the residents of this area were similar to those of the general Japanese population [10]. We performed epidemiological studies in every 10 years and followed up the participants every year. In 1999, the total population aged over 40 years in this district was 3463 (48.2% of men and 62.0% of women). A total of 1920 subjects (794 males and 1126 females; aged 40–95 years) were enrolled in this study. PA was measured by the Baecke PA questionnaire (BPAQ) [11–13]. In 2009, we measured PA by a simple questionnaire. Serum HGF levels were measured in 1999 and 2009 by the ELISA, by the same methods at a commercial-based laboratory (The Kyodo Igaku Laboratory, Fukuoka, Japan).

Baecke PA questionnaire (BPAQ)

We measured PA by BPAQ in 1999. The questionnaire consists of 16 questions organized into three sections: PA at work (Questions 1–8), sport during leisure time (Questions 9–12), and PA during leisure excluding sport (Questions 13–16) [5]. We defined total index as total PA index, which were summed up of work, sport, and leisure–time index. The questionnaire defined three levels of occupational/work PA, namely, low (e.g., clerical work, driving, shop keeping, teaching, studying, housework, medical practice and all other occupations with a university education), middle (e.g., farming, factory work, and carpentry), and high (e.g., dock work, construction work, and sport). Similarly, the questionnaire categorized sports into three levels: low (e.g., billiards, sailing, bowling and golf; average energy expenditure 0.76 MJ/h), middle (e.g., badminton, cycling, dancing, swimming, and tennis; average energy expenditure 1.26 MJ/h), and high (e.g., boxing, basketball, rugby, football, and rowing; average energy expenditure 1.76 MJ/h). A sport score was calculated from a combination of the intensity of the sport which was played, the amount of time per week playing that sport, and the proportion of the year in which the sport was played regularly. Questions in each of the three indices (work, sport, and leisure) were scored on a five-point Likert scale, ranging from “1 = never” to “5 = always” or “5 = very often”. Summing the three indices gives a total PA index [11, 12]. We applied a five-point Likert scales to all of the three indices and only in sports index, we applied the combinations of intensity and duration.

A simple PA questionnaire

We measured PA by a simple questionnaire in 2009. The questionnaire has four options (“1” is spending most of time at home, “2” is working with almost sitting or less playing sports, “3” is working with a lot of movement and standing or playing active sports, and “4” is doing hard works), and subjects chose one of them.

Data collection

Medical history, smoking habits, and alcohol intake were ascertained by a questionnaire. Smoking and alcohol intakes were classified as current habitual use or not. Height and weight were measured, and body mass index (BMI) was calculated as an index of obesity. Waist circumference was measured at the level of umbilicus in the standing position. Blood pressure (BP) was measured in the supine position twice at 3-min intervals using a standard sphygmomanometer. The second BP was taken after 5 deep breaths, and that was used for analysis.

Blood was drawn from the antecubital vein in the morning after a 12 h fast for determinations of lipids profiles (total cholesterol, triglycerides, high-density [HDL], and low-density lipoprotein cholesterol [LDL]), fasting plasma glucose (FPG), HbA1c (NGSP), insulin, serum urea nitrogen, creatinine, uric acid and serum HGF levels. Fasting blood samples were centrifuged within 1 h after collection. Serum HGF levels was measured by the ELISA [14] and the other chemistries were measured at a commercially available laboratory (Kyodo Igaku Laboratory, Fukuoka, Japan). The estimate of insulin resistance by homeostasis model assessment (HOMA) score was calculated with the formula: fasting insulin (µU/mL) × fasting glucose (mmol/L)/22.5 as described by Matthews et al. [15]. Insulin resistance was defined as HOMA ≥ 1.73 according to the diagnostic criteria used in Japan [16]. Estimated glomerular filtration rate (eGFR) was calculated according to the following estimation formula that has been recommended by the Japan Society of Nephrology: eGFR (mL/min/1.73²) = (194 × Scr⁻¹.094 × age⁻₀.287) × (0.739 for females) [17].

We divided into 2 groups (poor and good) by the median score of total PA index (median score was 7.75) in 1999, and also into 2 groups by a simple PA questionnaire in 2009. “Poor” was defined as subjects who chose “1” or “2”, and “good” was subjects who chose “3” or “4” of simple
questionnaires. Using these 4 PA groups, such as continuously low PA, increased PA, decreased PA, and continuously high PA, we compared their HGF levels in 10 years. We further investigated the development of hypertension, dyslipidemia, diabetes, and subjects who were suffering from CVD and cancer in 2009. The information was coded independently in accordance with the rules of the Seven Countries Study [9].

This study was approved by the Ukiha Branch of the Japan Medical Association, by the City Council of Tanushimarume, and by the Ethics Committee of Kurume University. All participants gave informed consent. All methods were carried out in accordance with relevant guidelines and regulations.

**Statistical analysis**

Because of skewed distributions, natural logarithmic transformations were performed for HOMA index triglycerides and γ-glutamyl transpeptidase (γ-GTP). Log-transformed values were used for the statistical calculation and converted to antilogarithm forms in the tables. Gender, the medications for hypertension, dyslipidemia, and diabetes, smoking habits, and alcohol intake were used as dummy variables. A paired \( t \) test was used to check the difference between two variables for the same subject.

First, we performed univariable and multivariable regression analyses for correlates of physical activity in 1999 and 2009 in the cross-sectional study. Second, we compared serum HGF levels by the 4 PA groups in 1999 and 2009 using analysis of co-variance (ANCOVA) adjusted for age and sex. Third, we compared the risk of development of hypertension, dyslipidemia, and diabetes, CVD, and cancer by 4 PA groups using ANCOVA adjusted for age and sex. Multiple comparisons were performed by Benjamini–Hochberg method. Finally, to compare the prevalence of CVD by 4 PA groups, we performed a logistic regression analysis adjusted for age and sex. Statistical significance was defined as a \( p \) value less than 0.05. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

**Results**

Of 1,920 participants, we excluded 600 subjects from whom we were not able to evaluate PA and HGF levels. We also excluded 417 subjects who did not undergo health check-ups in 2009. The remaining 903 (341 males and 562 females: mean age of 59.6 years) subjects were finally included in this analysis, and the relationships among PA and the HGF levels were examined.

**Cross-sectional study**

Demographic data for the 903 participants in 1999 and 2009 are shown in Table 1. The data indicated that most people were nonobese, normotensive, normolipidemic, and non-diabetic. Ten years later, BMI and waist circumference became larger. Heart rate, systolic and diastolic BPs were significantly higher in 2009 than in 1999. TC, TG, HDL, uric acid, FPG, HbA1c, HOMA index were also increased. The serum HGF levels were significantly higher in 2009 than in 1999. Although there is not a significant association between HGF and age both in 1999 and 2009, HGF levels slightly increase with age. Intrainsdividual changes in HGF showed 0.223 ± 0.085 ng/dL in 1999 and 0.293 ± 0.090 ng/dL in 2009 (\( n = 903, p < 0.001 \)). The uses of medications for hypertension, dyslipidemia, and diabetes were also increased. Frequency of alcohol intake was increased, whereas frequency of smoking was decreased.

**Activity measurements**

The mean total PA index in 1999 was 7.83, with work index of 3.36, sport index of 1.97, and leisure–time index of 2.50. The total PA index showed a normal distribution with a peak score of 7–8 (Fig. 1A). In 2009, 35% of the participants selected PA score 1 and 20% of them selected PA score 4 (Fig. 1B). Total number divided by the 4 physical activity groups in 1999 and 2009 are shown in Fig. 1C. Stable low was the most prevalent, and stable high was the second.

**Correlation between activity and comorbidities**

Univariable regression analysis for correlates of total PA index in 1999 is shown in Table 2. There was a significant relationship between total PA index and age \( (p = 0.034) \), male gender \( (p = 0.032) \), heart rate \( (p = 0.004; \text{ inversely}) \), HGF \( (p = 0.004; \text{ inversely}) \), and HOMA index \( (p = 0.026; \text{ inversely}) \). Subjects with diabetes and hypertension were not associated with total PA index. Univariable regression analysis for correlates of PA score in 2009 is shown in Table 3. There was a significant relationship between PA score and age \( (p < 0.0001; \text{ inversely}) \), male gender \( (p < 0.0001) \), BMI \( (p = 0.002) \), heart rate \( (p < 0.0001; \text{ inversely}) \), diastolic BP \( (p = 0.002) \), HGF \( (p = 0.001; \text{ inversely}) \), ALT \( (p = 0.023) \), γ-GTP \( (p = 0.011) \), eGFR \( (p < 0.0001) \), HOMA index \( (p = 0.040; \text{ inversely}) \), smoking
(p = 0.011), alcohol intake (p < 0.0001), medication for hypertension (p < 0.0001; inversely), medication for dyslipidemia (p = 0.001; inversely). Multivariable linear regression analysis for correlates of total PA index adjusted for demographics and lifestyle factors in 1999 is shown in Table 4. In the final model, total PA index was inversely associated with HGF (p = 0.0002, BH-adjusted p = 0.003) adjusted for age, sex, BMI, total cholesterol, systolic BP, HOMA index, and smoking. Multivariable linear regression analysis for correlates of PA score adjusted for demographics and lifestyle factors in 2009 is shown in Table 5. In the final model, there was a significant relationship between PA score and waist circumference (p = 0.020; inversely), heart rate (p = 0.0001; inversely), HGF (p = 0.003; inversely, BH-adjusted p = 0.014), γ-GTP (p = 0.041; inversely), eGFR (p = 0.001), uric acid (p = 0.004; inversely), FPG (p = 0.002), medication for hypertension (p = 0.007; inversely), medication for dyslipidemia (p = 0.001; inversely), alcohol intake (p < 0.0001), medication for hypertension (p < 0.0001; inversely), medication for dyslipidemia (p = 0.001; inversely). Multivariable linear regression analysis for correlates of total PA index adjusted for demographics and lifestyle factors in 1999 is shown in Table 4.

Table 1 Characteristics of the subjects at baseline (1999) and in 2009

| Variables | 1999 | 2009 | p       |
|-----------|------|------|---------|
| Age (year) | 59.6 ± 9.1 | 69.7 ± 9.1 | <0.0001 |
| Sex (% males) | 38.3 | 38.3 | – |
| Body mass index (kg/m²) | 23.2 ± 3.1 | 23.4 ± 3.3 | 0.0096 |
| Waist circumference (cm) | 76.8 ± 9.2 | 84.6 ± 9.7 | <0.0001 |
| Systolic blood pressure (mmHg) | 130.8 ± 19.6 | 134.6 ± 19.5 | <0.0001 |
| Diastolic blood pressure (mmHg) | 78.9 ± 11.4 | 81.0 ± 11.2 | <0.0001 |
| Heart rate (bpm/min) | 62.8 ± 9.2 | 64.8 ± 10.0 | <0.0001 |
| Hepatocyte growth factor (ng/ml) | 0.22 ± 0.08 | 0.29 ± 0.09 | <0.0001 |
| Estimated GFR (mL/min/1.73m²) | 58.1 ± 12.4 | 72.2 ± 16.6 | <0.0001 |
| Uric acid (µmol/L) | 291.5 ± 83.3 | 309.3 ± 83.3 | <0.0001 |
| Total cholesterol (mmol/L) | 5.2 ± 0.9 | 5.3 ± 0.9 | 0.0008 |
| HDL-cholesterol (mmol/L) | 1.5 ± 0.4 | 1.6 ± 0.4 | <0.0001 |
| LDL-cholesterol (mmol/L) | 3.2 ± 0.8 | 3.2 ± 0.8 | 0.1522 |
| Triglycerides (mmol/L) (mean (range)) | 1.1 (0.3–13.5) | 1.2 (0.1–9.4) | 0.0003 |
| HbA1c (%) (NGSP) | 5.6 ± 0.6 | 5.9 ± 0.6 | <0.0001 |
| Fasting plasma glucose (mmol/L) | 5.3 ± 0.8 | 5.6 ± 1.3 | <0.0001 |
| HOMA index (mean (range)) | 1.1 (0.2–24.9) | 1.4 (0.1–105.4) | <0.0001 |
| Smoking (% yes) | 13.6 | 7.7 | <0.0001 |
| Alcohol intake (% yes) | 22.4 | 40.3 | <0.0001 |
| Medication for hypertension (% yes) | 15.4 | 47.5 | <0.0001 |
| Medication for dyslipidemia (% yes) | 4.6 | 42.3 | <0.0001 |
| Medication for diabetes (% yes) | 1.9 | 11.3 | <0.0001 |
| Total index (max score 15) | 7.83 ± 1.18 | – | – |
| a. Work index (max score 5) | 3.36 ± 0.67 | – | – |
| b. Sport index (max score 5) | 1.97 ± 0.57 | – | – |
| c. Leisure-time index (max score 5) | 2.50 ± 0.73 | – | – |
| Physical activity score n (% | 1 (mean (range)) | – | 304 (34.7) | – |
| 2 (mean (range)) | – | 152 (17.3) | – |
| 3 (mean (range)) | – | 242 (27.6) | – |
| 4 (mean (range)) | – | 179 (20.4) | – |

Data are mean ± standard deviation, geometric mean, range, or percent. Total index = Total physical activity index (a + b + c) 
GFR glomerular filtration rate. HDL-C high-density lipoprotein cholesterol, LDL-C Low-density lipoprotein cholesterol, HbA1c glycosylated hemoglobin A1c, HOMA homeostasis model assessment

*These variables were represented in the original scale after analysis using log (natural) transformed values.
Fig. 1  Distribution of PA levels.  
A Distribution of the PA index (Total index, BPAQ) in 1999.  
B Distribution of the simple PA questionnaire in 2009.  
C Participants number divided by the four physical activity groups in 1999 and 2009.
dyslipidemia ($p = 0.008$; inversely) adjusted for age, sex, BMI, total cholesterol, systolic BP, HOMA index, and smoking.

**Prospective study**

Figure 2A shows the serum HGF levels in 2009 divided by the 4 PA groups. The serum HGF levels of increased PA group were significantly lower than those of stable low PA group ($p = 0.038$). The serum HGF levels of stable high PA group were significantly lower than those of decreased PA group ($p = 0.019$) adjusted for age and sex (Fig. 2B). Figure 2C shows the development of CVD by the four physical activity groups. The prevalence of CVD development in increased PA group was significantly lower than that in stable low PA group ($p = 0.021$). After adjustment for age and sex, the prevalence of CVD development in increased PA group was still significantly lower than that of stable low PA group ($p = 0.012$) (Fig. 2D). Logistic regression analysis for correlates of the development of CVD is shown in Table 6. The adjusted odds ratio for the development of CVD in increased PA group compared to stable low PA group was 0.29 (95% CI 0.11–0.81).

### Table 2
Univariable linear regression analysis for correlates of total physical activity index in 1999

| Variables                         | β   | SE   | $p$  |
|----------------------------------|-----|------|------|
| Age (year)                       | 0.009 | 0.004 | 0.034 |
| Sex (males = 0, females = 1)     | −0.180 | 0.081 | 0.032 |
| Body mass index (kg/m²)          | 0.001 | 0.013 | 0.978 |
| Waist circumference (cm)         | 0.005 | 0.004 | 0.243 |
| Systolic blood pressure (mmHg)   | 0.001 | 0.002 | 0.788 |
| Diastolic blood pressure (mmHg)  | 0.001 | 0.004 | 0.982 |
| Heart rate (bpm/min)             | −0.012 | 0.004 | 0.004 |
| Hepatocyte growth factor (ng/ml) | −1.642 | 0.462 | 0.001 |
| Estimated GFR (ml/min/1.73m²)    | 0.001 | 0.003 | 0.711 |
| Uric acid (µmol/L)               | 0.022 | 0.029 | 0.441 |
| Total cholesterol (mmol/L)       | −0.002 | 0.001 | 0.140 |
| HDL-cholesterol (mmol/L)         | 0.002 | 0.003 | 0.589 |
| LDL-cholesterol (mmol/L)         | −0.002 | 0.001 | 0.174 |
| Triglycerides (mmol/L)           | −0.071 | 0.076 | 0.352 |
| HbA$_{1c}$ (%) (NGSP)            | 0.012 | 0.063 | 0.844 |
| Fasting plasma glucose (mmol/L)  | 0.001 | 0.003 | 0.679 |
| HOMA-index†                      | −0.138 | 0.062 | 0.026 |
| Smoker (%), yes                  | −0.036 | 0.115 | 0.755 |
| Alcohol intake (%), yes          | 0.181 | 0.094 | 0.055 |
| Medication for hypertension (%), yes | 0.127 | 0.109 | 0.243 |
| Medication for dyslipidemia (%), yes | −0.219 | 0.189 | 0.247 |
| Medication for diabetes (%), yes | 0.258 | 0.290 | 0.372 |

$SE$ standard deviation, $GFR$ glomerular filtration rate, $HDL-C$ high-density lipoprotein cholesterol, $LDL-C$ low-density lipoprotein cholesterol, $HbA$_{1c} glycosylated hemoglobin $A_{1c}$, $HOMA$ homeostasis model assessment

†These variables were represented in the original scale after analysis using log (natural) transformed values

### Table 3
Univariable linear regression analysis for correlates of physical activity score in 2009

| Variables                         | β   | SE   | $p$  |
|----------------------------------|-----|------|------|
| Age                              | −0.038 | 0.004 | <0.0001 |
| Sex (males = 0, females = 1)     | −0.489 | 0.079 | <0.0001 |
| Body mass index                  | 0.036 | 0.012 | 0.002 |
| Waist circumference              | 0.002 | 0.004 | 0.639 |
| Systolic blood pressure          | −0.001 | 0.002 | 0.801 |
| Diastolic blood pressure         | 0.011 | 0.004 | 0.002 |
| Heart rate (bpm/min)             | −0.020 | 0.004 | <0.0001 |
| Hepatocyte growth factor         | −1.500 | 0.432 | 0.001 |
| AST                              | 0.001 | 0.004 | 0.988 |
| ALT                             | 0.001 | 0.003 | 0.023 |
| γ-GTP†                           | 0.158 | 0.062 | 0.011 |
| Estimated GFR                    | 0.014 | 0.002 | <0.0001 |
| Uric acid                        | 0.008 | 0.028 | 0.766 |
| Total cholesterol                | 0.001 | 0.001 | 0.754 |
| HDL-cholesterol                  | −0.003 | 0.003 | 0.301 |
| LDL-cholesterol                  | 0.001 | 0.001 | 0.500 |
| Triglycerides†                   | 0.112 | 0.077 | 0.145 |
| HbA$_{1c}$                       | 0.102 | 0.060 | 0.089 |
| Fasting plasma glucose           | 0.002 | 0.002 | 0.192 |
| HOMA-index†                      | −0.084 | 0.041 | 0.040 |
| Smoking                          | 0.369 | 0.144 | 0.011 |
| Alcohol intake                   | 0.438 | 0.078 | <0.0001 |
| Medication for hypertension      | −0.334 | 0.077 | <0.0001 |
| Medication for dyslipidemia      | −0.263 | 0.079 | 0.001 |
| Medication for diabetes          | −0.050 | 0.123 | 0.685 |

AST aspartate aminotransferase, ALT alanine aminotransferase, γ-GTP gamma glutamyl transferase, GFR glomerular filtration rate, HDL-C high-density lipoprotein cholesterol, LDL-C low-density lipoprotein cholesterol, $HbA$_{1c} glycosylated hemoglobin $A_{1c}$, $HOMA$ homeostasis model assessment

†These variables were represented in the original scale after analysis using log (natural) transformed values
Discussion

The present study demonstrated that improvement of PA levels was associated with the decrease of HGF levels and CVD development. Furthermore, there have been previously no reports regarding the associations between serum HGF level and improvement of PA among 4 PA groups, such as stable low PA, increased PA, decreased PA, and stable high PA. These results suggest that HGF levels may be a useful indicator to reach the enough improvement of PA.

It is interesting to note that HGF level in increased PA group was the lowest among the 4 PA groups (Fig. 2A, B). These results suggest that low PA at baseline is not too late and that there may be enough time to decrease HGF levels. In addition, it was also expected that the prevalence of CVD development in increased PA group was significantly lower than that in stable low PA group (Fig. 2C, D).

Recent epidemiological reports from ARIC (Atherosclerosis Risk in Communities) study [18] suggested that maintaining recommended activity levels was associated with the lowest heart failure (HF), whereas those with any decrease in PA category had an increased HF risk. The mechanisms how PA changes were associated with HF risk are not fully understood. Increased levels of PA are associated with improved metabolic profiles, including decreases in FPG and BMI and increases in HDL-cholesterol. Because serum HGF levels were strongly associated with the metabolic files [3], our study may provide a key clue.

The accumulated evidence [19–22] has revealed that HGF is an independent predictor of coronary heart disease, heart
failure, stroke and progression of atherosclerosis. Likewise, higher serum levels of HGF have been found in individuals with CVD risk factors, such as obesity, hypertension, diabetes, and MetS, which were associated with low PA. Favorable cardiovascular health was significantly associated with lower HGF levels in the Multi-Ethnic Study of Atherosclerosis (MESA) [23]. Although there is no report of the potential role of mediation of HGF in the association of PA and CVD/MetS-related diseases, HGF can be a key player between PA and CVD/MetS-related diseases.

Because HGF is a member of the endothelium-specific growth factors, it is possible that HGF may play a role in CVD. HGF is elevated in CVD as a response to endothelial damage [21]. Interestingly, transforming growth factor (TGF)-β significantly decreased HGF secretion from endothelial cell [24, 25]. In human vascular smooth muscle cells, TGF-β and angiotensin-II suppressed local HGF production in a dose-dependent manner [26]. Nakano and Morishita, et al. [26] studied the role of angiotensin II in the regulation of the HGF system in vivo using a balloon injury model. Given the strong mitogenic activity of HGF on endothelial cells, increased local HGF production by blockade of angiotensin II may enhance reendothelialization after balloon injury. Downregulation of the local vascular

Table 5 Multivariable linear regression analysis for correlates of physical activity score in 2009

| Variables                        | Model 1 |          |          |          |          |          |          |          |          |          |          |          |
|---------------------------------|---------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|
|                                 | $\beta$ (SE) | p       | $\beta$ (SE) | p       | $\beta$ (SE) | p       | $\beta$ (SE) | p       |
| Body mass index                 | 0.020 (0.011) | 0.066  | –        | –        | –        | –        | –        |
| Waist circumference             | 0.001 (0.004) | 0.940  | –0.016 (0.007) | 0.014  | –0.015 (0.007) | 0.020  |
| Systolic blood pressure         | 0.001 (0.002) | 0.702  | 0.001 (0.002) | 0.965  | –        | –        |
| Diastolic blood pressure        | 0.002 (0.003) | 0.634  | 0.001 (0.003) | 0.925  | 0.001 (0.005) | 0.945  |
| Heart rate                      | –0.015 (0.004) | <0.0001 | –0.015 (0.004) | <0.0001 | –0.014 (0.004) | 0.0001 |
| Hepatocyte growth factor        | –1.177 (0.413) | 0.004  | –1.257 (0.414) | 0.003  | –1.242 (0.422) | 0.003  |
| Estimated GFR                   | 0.008 (0.002) | 0.002  | 0.008 (0.002) | 0.001  | 0.008 (0.002) | 0.001  |
| Uric acid                       | –0.068 (0.029) | 0.017  | –0.086 (0.029) | 0.004  | –0.085 (0.030) | 0.004  |
| AST                             | –0.002 (0.003) | 0.488  | –0.002 (0.003) | 0.528  | –0.002 (0.003) | 0.582  |
| ALT*                            | –0.002 (0.003) | 0.602  | –0.002 (0.003) | 0.454  | –0.002 (0.003) | 0.524  |
| γ-GTP†                          | –0.121 (0.064) | 0.057  | –0.142 (0.064) | 0.027  | –0.134 (0.065) | 0.041  |
| Total cholesterol               | 0.001 (0.001) | 0.666  | –        | –        | –        | –        |
| HDL-cholesterol                 | –0.001 (0.003) | 0.714  | 0.001 (0.003) | 0.902  | –0.001 (0.003) | 0.836  |
| LDL-cholesterol                 | 0.001 (0.001) | 0.442  | 0.001 (0.002) | 0.584  | 0.001 (0.002) | 0.620  |
| Triglycerides†                  | 0.025 (0.072) | 0.730  | –0.030 (0.077) | 0.701  | 0.005 (0.082) | 0.952  |
| HbA1c                           | 0.075 (0.056) | 0.177  | 0.062 (0.056) | 0.273  | 0.080 (0.057) | 0.165  |
| Fasting plasma glucose          | 0.003 (0.002) | 0.033  | 0.003 (0.002) | 0.046  | 0.006 (0.002) | 0.002  |
| HOMA-index†                     | –0.002 (0.039) | 0.969  | –0.034 (0.042) | 0.414  | –        | –        |
| Smoking                         | –0.164 (0.144) | 0.257  | –0.150 (0.144) | 0.298  | –        | –        |
| Alcohol intake                  | 0.122 (0.086) | 0.157  | 0.117 (0.086) | 0.173  | 0.116 (0.087) | 0.187  |
| Medication for hypertension     | –0.166 (0.075) | 0.027  | –0.196 (0.076) | 0.010  | –0.222 (0.082) | 0.007  |
| Medication for dyslipidemia     | –0.186 (0.075) | 0.013  | –0.220 (0.077) | 0.004  | –0.206 (0.077) | 0.008  |
| Medication for diabetes         | –0.102 (0.114) | 0.369  | –0.122 (0.115) | 0.286  | –0.120 (0.116) | 0.303  |

Model 1: adjusted for age and sex
Model 2: adjusted for Model 1 + body mass index, total cholesterol, and systolic blood pressure
Model 3: adjusted for Model 2 + HOMA index, and smoking

SE standard deviation, GFR glomerular filtration rate, AST aspartate aminotransferase, ALT alanine aminotransferase, γ-GTP gamma glutamyl transferase, HDL-C high-density lipoprotein cholesterol, LDL-C low-density lipoprotein cholesterol, HbA1c glycated hemoglobin A1c, HOMA homeostasis model assessment
HGF system by TGF-β and vascular angiotensin may play an important role in the pathogenesis of CVD [26].

Reports from the MESA [27] indicated that higher average PA levels and higher PA increases over an average of 10 year period were associated with a more eccentric-type of left ventricular remodeling pattern. Recent epidemiological study [28] suggested that a positive association between several circulating vascular growth factors including HGF and cardiac remodeling was shown with the known biological effects of these pro- and anti-angiogenic factors on the myocardium and conduit arteries. Although the target diseases were not completely the same as ours, two clinical studies [29, 30] have shown the significant relationship between HGF and left ventricular remodeling, which may be explained by the correlation between PA levels and circulating HGF.

**Strengths and limitations**

This study has several strengths. We have measured PA and serum HGF levels twice in 1999 and 2009. We used a population-based sample with robust longitudinal follow-up of disease outcomes, such as CVD. Many baseline characteristics including conventional coronary risk factors were used to examine a relationship with PA levels. This study also has several limitations. First, we used different questionnaires to assess the levels of PA. We measured PA by BPAQ in 1999, and by a simple PA questionnaire in 2009. Second, self-report PA questionnaires were used, thereby, increasing recall bias. Third, we do not have any data regarding the detailed educational and income levels. Finally, the present study was performed in a single Japanese population and our conclusions may not be generalizable to other populations with different lifestyles and genetic backgrounds.

In conclusion, the present study clearly demonstrated that improvement of PA levels was associated with reduced HGF levels and CVD development in a general Japanese population. Serum HGF levels may be a useful biomarker to detect the PA improvement in the clinical settings.
Table 6  Odds ratios for the development of CVD during the period from 1999 to 2009 according to the subgroups defined by physical activity levels in 1999 and in 2009

| Physical activity levels | Number of events/subjects | OR (95% CI) | p value | Adjusted for age and sex OR (95% CI) | p value |
|-------------------------|---------------------------|-------------|---------|-------------------------------------|---------|
| Stable low              | 23/248                    | 1 (reference) |         | 1 (reference)                       |         |
| Increased               | 5/182                     | 0.28 (0.10–0.074) | 0.0312 | 0.29 (0.11–0.81)                   | 0.0694  |
| Decreased               | 17/197                    | 0.92 (0.48–1.78) | 0.0717 | 0.73 (0.37–1.44)                   | 0.3223  |
| Stable high             | 11/225                    | 0.50 (0.24–1.06) | 0.5203 | 0.49 (0.23–1.07)                   | 0.5958  |

CVD cerebro-cardiovascular disease, OR odds ratio

Acknowledgements  AS was primary investigator and performed this examination. HA, ME, AF, YN, NM, MY, and HS, planned and performed this study. KM performed the statistical analysis. YF designed this study and he is a head of the department supervisor. All the authors read and approved the final manuscript. We are grateful to the members of the Japan Medical Association of Ukiha, the elected officials and residents of Tanushimaru, and the team of cooperating physicians for their help in performing the health examinations. This study was supported in part by the Kimura Memorial Heart Foundation (Fukuoka, Japan).

Declarations

Conflict of interest  A. Sakaue, H. Adachi, M. Enomoto, A. Fukami, Y. Nohara, N. Morikawa, M. Yamamoto, H. Sato, K. Murotani, and Y. Fukumoto declared no potential conflict of interest with respect to the research, authorship, and/or publication of this article.

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