Effects of creatine supplementation and exercise training on fitness in men 55–75 yr old

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Eijnde, Bert O., Marc Van Leemputte, Marina Goris, Valery Labarque, Youri Taes, Patricia Verbessem, Luc Vanhees, Monique Ramaekers, Bart Vanden Eynde, Reinout Van Schayckenbergh, René Dom, Erik A. Richter, and Peter Hespel. Effects of creatine supplementation and exercise training on fitness in men 55–75 yr old. J Appl Physiol 95: 818–828, 2003. First published March 28, 2003; 10.1152/japplphysiol.00891.2002.—The effect of oral creatine supplementation (CR; 5 g/day) in conjunction with exercise training on physical fitness was investigated in men between 55 and 75 yr of age (n = 46). A double-blind randomized placebo-controlled (PL) trial was performed over a 6-mo period. Furthermore, a subgroup (n = 20) completed a 1-yr follow-up. The training program consisted of cardiorespiratory endurance training as well as moderate resistance training (2–3 sessions/wk). Endurance capacity was evaluated during a maximal incremental bicycle ergometer test, maximal isometric strength of the knee-extensor muscles was assessed by an isokinetic dynamometer, and body composition was assessed by hydrostatic weighing. Furthermore, in a subgroup (PL: n = 13; CR: n = 12) biopsies were taken from m. vastus lateralis to determine total creatine (TCr) content. In PL, 6 mo of training increased peak oxygen uptake rate (+16%; P < 0.05), whereas percent body fat slightly decreased (~1.2%; P < 0.05). The training intervention did not significantly change either maximal isometric strength or body weight. The responses were independent of CR. Still, compared with PL, TCr was increased by ~5% in CR, and this increase was closely correlated with initial muscle creatine content (r = −0.78; P < 0.05). After a 1-yr follow-up, muscle TCr was not higher in CR than in PL. Furthermore, the other measurements were not affected by CR. It is concluded that long-term creatine intake (5 g/day) in conjunction with exercise training does not beneficially impact physical fitness in men between 55 and 75 yr of age.

elderly; muscle strength; endurance capacity

A PRIMARY STRATEGY TO OPTIMIZE HEALTH in older people is to prevent potential medical problems from reaching an overt clinical state (29). In this respect, research over the last 20–30 yr has clearly shown that increasing the level of physical activity is an effective intervention to alleviate the normal deterioration of health-related fitness parameters (35), which include functional capacity of the musculoskeletal and cardiovascular system, body composition, and metabolic health (8). Resistance training can reduce the pace of age-related muscle atrophy and the concomitant decline of muscular functional capacity (19, 21, 28). The latter is very critical to maintain the ability to perform activities of daily living. Furthermore, endurance exercise training can enhance cardiorespiratory fitness in older people (14). Endurance training also reduces cardiovascular risk by beneficially impacting cardiovascular risk factors such as adverse blood lipid profile, high blood pressure, and impaired glucose tolerance due to peripheral insulin resistance (29, 50). Thus published literature provides strong evidence to suggest that both aerobic endurance and resistance training can beneficially impact physical fitness in older people.

Another intervention that might contribute to enhance physical fitness in older people is oral creatine supplementation (CR). The potential of oral creatine (Cr) intake to increase muscle Cr content, and thereby enhance muscular performance during short maximal exercise over repeated bouts in the young, has been extensively documented over the last 10 yr (47, 53). The finding that CR can stimulate the beneficial effects of resistance training on muscle volume and functional capacity, at least in young healthy subjects (5, 27, 34, 48, 50), is interesting in the context of the preservation of muscle functional capacity in the elderly. Furthermore, consistent with the observations in young healthy subjects, CR has been found to enhance muscular functional capacity in patients afflicted by neuromuscular diseases (45, 51, 52) as well as in cardiac patients (11, 22). It has been suggested that older people might respond better to CR than young people,

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because they may have a lower muscle Cr content (46). However, literature data are not consistent with regard to the latter issue (12, 31, 36, 37), and a recent study (41) has even shown Cr content in muscles from older people to be higher than in younger people. Furthermore, some earlier studies have found the effects of CR in conjunction with resistance training on muscular performance capacity in the elderly to be either absent (7, 42), small (11), or moderate (10). However, the intervention periods in the latter studies were short (7 days to 14 wk) relative to the need for long-term physical activity in the older population. Moreover, the training interventions used in the above studies involved only heavy resistance training. However, in older persons, a mixed training program combining both cardiorespiratory stimulation and moderate resistance training probably is more optimal than selective high-load weight training (3, 29). Therefore, to improve our understanding of the efficacy of Cr intake as a potential ergogenic aid in the older population, it is warranted to evaluate the effects of long-term Cr intake in conjunction with an exercise training program involving both endurance training and moderate resistance training (47).

Long-term Cr intake currently is being promoted as a health-enhancing substance. At present, however, no study has investigated the impact of long-term (12 mo) low dose (5 g/day) Cr intake on a variety of safety parameters. Because knowledge regarding the occurrence of adverse side effects after the supplementary intake of any “ergogenic” substance is essential, it is necessary to investigate this matter. Furthermore, some (1, 17), but not all (49), studies have reported CR in combination with resistance training to have a cholesterol-lowering effect. Because of the high prevalence of elevated blood cholesterol at older age, it is therefore warranted to further investigate the potential cholesterol-lowering effect after long-term Cr intake.

Therefore, the purpose of the present study was to evaluate whether long-term Cr intake in conjunction with exercise training in older men is safe and can have a beneficial impact on physical fitness, including muscle strength and cardiorespiratory endurance.

METHODS

Subjects

Subjects were recruited from the staff (active or retired) at the local university. Men older than 55 yr were invited to participate in a meeting aimed to explain the purpose and details of the study protocol. Within the next week, 57 subjects, who met the inclusion criteria, volunteered to participate in the study. After being informed of all the experimental procedures to be undertaken, they gave their written, informed consent and were enrolled in the study. Inclusion criteria were 1) men between 55 and 75 yr of age; 2) no participation in strength training for at least 5 yr; 3) participation in low-intensity physical activity, such as gardening and walking, for <4 h/wk; and 4) no history of oral Cr intake. All volunteers underwent a preliminary clinical examination and were submitted to an electrocardiogram (ECG)-controlled maximal exercise test. Exclusion criteria on admission were prehistory of kidney disease, albuminuria, consistent intake of any medication known to impair exercise capacity, and any disease contraindicating high-intensity exercise training. From the 57 volunteers screened, 11 were excluded because of a significant ST depression (1.5 mm or more; n = 4), complicated ventricular arrhythmias (n = 3), arterial fibrillation (n = 1), hypertension (n = 2), and ECG-diagnosed posterior myocardial infarction (n = 1). Subjects were asked to avoid changes in their diet and level of physical activity (except for the fitness training program prescribed by the study protocol), and to maintain constant living habits during the period of the study.

Study Protocol

The local ethics committee approved the study protocol. A double-blind study was performed over a 1-yr period that involved two phases (phase I: 0–6 mo; phase II: 6 mo to 1 yr). Baseline measurements were performed on 3 separate days, each separated by a 2-day interval. On day 1, after a standardized warm-up, subjects performed an exercise test on an isokinetic dynamometer to evaluate maximal and fatigue of the knee extensor muscles. Test-retest reliability for these torque measurements was 0.93 (intraclass correlation [2,1]). Immediately afterward, body composition was assessed in the seated position by hydrostatic weighing. On day 2, subjects reported to the laboratory for a maximal incremental exercise test on an electromagnetically braked bicycle ergometer. Finally, on day 3, the subjects reported to the laboratory in the morning after an overnight fast. A blood sample was taken from an antecubital vein into heparinized tubes (Vacutainer) for clinical biochemistry. Furthermore, in a subgroup of subjects, a muscle biopsy was taken from the vastus lateralis muscle under local anesthesia for biochemical and histochromatical analysis on day 4. After the baseline measurements, subjects were coupled into pairs that were matched for age, maximal isometric knee-extension torque, and peak oxygen uptake (Vo2peak). Thereafter, each pair was assigned, in a double-blind manner and by an independent investigator who was otherwise not involved in the study, to either a PL (n = 23; age: 62.2 ± 1.3 yr; body weight: 81.3 ± 2.5 kg) or a CR (n = 23; age: 63.9 ± 1.1 yr; body weight: 79.2 ± 2.3 kg) group.

After baseline measurements, subjects were enrolled in a well-controlled and supervised fitness training program. The training-program aimed to increase cardiorespiratory fitness as well as enhance strength of the abdominal and back muscles and the primary peripheral muscle groups. During phase I, subjects were instructed to participate in 10 training sessions per 4-wk “window.” To ensure adequate recovery between training sessions, training sessions were interspersed by at least 1 rest day. Each training session (~75 min) started with two endurance exercise bouts, which first involved bicycle ergometry (12 min) and thereafter treadmill walking/jogging or rowing ergometry (12 min). To monitor the training workload, exercise intensity was controlled by heart rate monitoring. Exercise intensity was initially set at 65% of the individual heart rate reserve (Karvonen formula) and was increased gradually to 80% of heart rate reserve toward the end of the training period. The bicycle ergometers and treadmills used (Technogym) automatically estimated the number of calories spent during the exercise performed. These values were noted in the individual training diary. For the rowing ergometry, resistance was fixed and the estimated distance covered was noted in a training diary. The latter values were later used as a global measure to compare the amount of endurance work performed between groups. After
the endurance training bouts, the subjects started a moderate-resistance weight training session. They performed seven exercises (sit-ups, arm curl, back extension, leg extension, leg press, vertical row, and lateral pull on Technogym gym apparatus). Each exercise consisted of two series of 30 repetitions at 30-repetition maximum (RM) workload. To monitor training workload, subjects were instructed to note the resistance used (in kg) in their training diary for the two series of each exercise.

From the start of the training program, CR received 5 g of Cr monohydrate tablets per day, whereas the placebo-controlled (PL) group received placebo tablets. On nontraining days, subjects ingested one tablet before breakfast, three before lunch, and one before dinner. However, on training days, the 3-g dose was to be ingested immediately after the training session. Hence, before lunch and dinner on morning training days, and before breakfast and lunch on evening training days, subjects ingested one tablet. After 3 and 6 mo, and at least 48 h after their last training session, subjects returned to the laboratory to participate in the same measurements as at baseline. However, at 3 mo, no muscle biopsy was taken. At each occasion, the tests were performed at the same time of day and by the same investigator. At the end of phase I, subjects were asked to either engage for an additional 6 mo of follow-up (phase II) or to withdraw from the study. Thirty-six subjects agreed to continue participating in the study (PL: n = 21, age: 61.6 ± 1.3 yr; CR: n = 15, age: 65.3 ± 1.3 yr) and 10 withdrew (PL: n = 2; CR: n = 8). Thus, in phase II of this study, subjects were not randomly selected but instead voluntarily chose to remain in the study. To enhance training compliance on the one hand and to meet the expectations by the subjects on the fitness training on the other hand, the training protocol was slightly adapted. Min-imum training rate was reduced from 10 to 8 sessions per week. The training workload, subjects were instructed to note the resist-
ance used (in kg) in their training diary for the two series of each exercise.

Maximal Exercise Testing and Spirometry

The maximal exercise tests on an electromagnetically braked bicycle ergometer (Ergometrics model 800S, Bitz, Germany) were performed in a laboratory where room temperature was stabilized at 18–22°C. At the occasion of the first test, seat height was noted and reproduced for all subsequent tests. Subjects first rested for 10 min in the upright seated position on the ergometer, where their blood pressure was measured by using an automated sphygmomanometer (model STBP-780, Colin, Komaki, Japan). Thereafter, the exercise test was started at an initial workload of 20 W, which was increased by 20 W every minute until volitional exhaustion. At each occasion, the tests were performed at the same time of day and by the same investigator. None of the study results were disclosed to either the subjects or to the investigators until the end of the entire study.

Maximal voluntary torque and power of the knee extensors was evaluated on an isokinetic dynamometer that consisted of a computer-controlled asynchronous electromotor (AMK Dynasyn, 19 kW), instrumented with a torque transducer (Lebow, maximal torque 565 N·m, 0.05% precision). The exercise test consisted of unilateral knee extensions performed in a semiupright sitting position on the dynamometer. After a 5-min standardized warm-up, the subjects performed two voluntary maximal isometric contractions (3 s), interspersed by 2-min rest intervals, at knee angles of 90, 110, and 130°, respectively. Maximal isometric torque (in N·m) was obtained from the smoothed curve of the static torque and was calculated as the average of the three knee angles (90, 110, and 130°). Thereafter, subjects performed two bouts of 30 dynamic maximal voluntary knee extensions, interspersed by a 2-min rest interval, at a constant velocity of 180°/s, starting from 90° to full extension (180°). After each contraction, the leg was returned (180°/s) passively to the starting position from which the next contraction was immediately initiated. Torque and angular velocity were measured during each contraction and were simultaneously digitized (250 Hz) by an on-line computer.

Body Composition

Body composition was assessed in the seated position by hydrostatic weighing. Residual lung volume was measured by the helium-dilution technique, and gastrointestinal tract air volume was assumed to be 150 ml. Body density was converted to percent body fat by using Siri’s equation (43), where percent body fat is equal to [4.95/density − 4.5] × 100.

Muscle Biochemistry and Histochemistry

Muscle samples were obtained from the vastus lateralis muscle of the right leg by using the needle biopsy technique. Incisions were made through the skin and muscle fascia after the administration of 2–3 ml of local anesthesia (lidocaine, 1%). After removal from the limb, a piece of each muscle biopsy was immediately freed from blood and visible connective tissue, rapidly frozen in liquid nitrogen, and stored at −80°C for subsequent biochemical analysis. The remaining muscle was mounted in embedding medium, frozen in isopentane, cooled to its freezing point in liquid nitrogen, and stored at −80°C until analyses were performed at a later date. For muscle substrate assays, muscle samples were freeze-dried. Thereafter, a portion (3–5 mg) of each sample was dissected free of visible blood and connective tissue. Muscle ATP, free Cr, and phosphocreatine (PCr) contents were analyzed from perchloric acid precipitated extractions by using standard fluorometric assays (6). Because muscle ATP content normally does not change as a result of the interventions or treatments used, free Cr and PCr content was corrected for the individual mean ATP content over the time points. Total Cr (TCr) content was calculated by summing free Cr and PCr content. For the histochemical analyses, serial transverse sections (10 μm) were cut from the
biopsies with a microtome at −20°C and stained for myofibrillar ATPase to identify fiber types (9).

**Clinical Chemistry**

Routine blood and urine clinical screening tests were performed during the course of the study. The serum samples were immediately transferred to a local routine clinical biochemistry laboratory for determination of white and red blood cells, hemoglobin, hematocrit, mean cell volume, mean cell hemoglobin, mean cell hemoglobin concentration, and red cell distribution width by using a Beckman-Coulter autoanalyzer, and of glutamate oxalate transaminase, glutamate pyruvate transaminase, alkaline phosphatase, Cr kinase, urea, and urate by using a Hitachi autoanalyzer both running on Roche diagnostic reagents. All plasma samples and a fraction of the 24-h urine samples were stored at −20°C to be analyzed at the end of the study. Plasma and urinary Cr concentrations were measured by a standard enzymatic fluorometric assay (6). Plasma and urinary creatinine concentration were assayed by a rate-blanked kinetic Jaffé-based method (alkalic picrate, Roche Diagnostics).

In the subgroup that completed the 1-yr follow-up, we also measured blood lipids. Total cholesterol, triglycerides, and high-density lipoprotein (HDL) cholesterol were analyzed using a cholesterol oxidase-based method, after which low-density lipoprotein (LDL) cholesterol was calculated according to the following formula: total cholesterol − HDL-cholesterol − (triglycerides/5).

**Statistical Analyses**

Separate statistical analyses were performed on the data in the total group of subjects (phase I, 6-mo follow-up; n = 46) and on the subgroup that also participated in phase II of the study (phase I and II, 1-yr follow-up; n = 20). Missing data (≤5% for the muscle histochemistry and blood biochemistry data; ≤2% for all other data) were imputed according to the null hypothesis. **Phase I** data were analyzed according to the "intention-to-treat" principle. **Phase I and II** data were analyzed according to the "as-treated" principle. Treatment effects were evaluated by using two-way analyses of variance that were covariate adjusted for the baseline value (Statistica, Statsoft, Tulsa, OK). When appropriate, Tukey’s post hoc tests were applied. In addition, we also performed a one-way analysis of variance to compare within the groups the baseline values with the values obtained after 3, 6, and 12 mo of follow-up. The relationship between variables was calculated by using Pearson’s correlation coefficient. Statistical significance was taken at a probability level of P < 0.05. All data are expressed as means ± SE.

**RESULTS**

**Training Compliance**

**Six-month follow-up.** The number of training sessions completed was similar between PL (56 ± 3 training sessions) and CR (59 ± 2 training sessions). Furthermore, the total number of calories spent in walking and/or running (PL: 4,420 ± 370 kcal; CR: 4,340 ± 210 kcal) and bicycling (PL: 6,880 ± 410 kcal; CR: 6,560 ± 280 kcal), as well as the total estimated distance covered during rowing ergometry (PL: 56 ± 5 km; CR: 58 ± 4 km) did not differ between groups. Workloads for leg extension and arm curl, the two exercises that were obligatory throughout the training period, were similar between PL and CR both during the initial 4 wk of the 6-mo training period (PL leg extension: 27 ± 2 kg, arm curl: 16 ± 1 kg; CR leg extension: 29 ± 2 kg, arm curl: 16 ± 1 kg), increasing to the period (PL leg extension: 49 ± 5 kg, arm curl: 27 ± 2 kg; CR leg extension: 49 ± 5 kg, arm curl: 26 ± 2 kg) during the final 4 wk (P < 0.05).

**One-year follow-up.** The number of training sessions completed during phase I was 67 ± 2 in both PL and CR. Furthermore, the number of calories spent in walking and/or running (PL: 5,160 ± 570 kcal; CR: 4,530 ± 260 kcal) and bicycling (PL: 8,200 ± 520 kcal; CR: 7,490 ± 320 kcal), and the distance covered during rowing ergometry (PL: 68 ± 9 km; CR: 69 ± 5 km) did not vary between groups. During phase II of the study, minimum training rate was reduced from 10 to 8 sessions per 4-wk training cycle. Hence, compared with phase I, the number of training sessions completed decreased (PL: 41 ± 3 training sessions; CR: 46 ± 2 training sessions). Compared with PL (3,020 ± 420 kcal), the number of calories spent in walking and/or running was higher (P < 0.05) in CR (3,940 ± 280 kcal). However, neither the number of calories spent in cycling (PL: 6,220 ± 600 kcal; CR: 6,430 ± 530 kcal) nor the distance covered during rowing (PL: 59 ± 7 km; CR: 56 ± 6 km) was different between PL and CR. Workloads for leg extension and arm curl during the first 4-wk training period were similar in PL (leg extension: 28 ± 3 kg; arm curl: 17 ± 2 kg) and CR (leg extension: 31 ± 3 kg; arm curl: 16 ± 1 kg). Six months of training increased leg extension and arm curl workloads by ~75% in either group. At month 12, compared with baseline, leg extension workload was increased by another ~15% in both PL and CR (P < 0.05), whereas arm curl workload was decreased by ~20% in both groups (P < 0.05).

**Side Effects**

All subjects underwent cardiological screening, including stress ECG testing, before the start of the study. Still, during phase I of the study, five subjects (4 in CR vs. 1 in PL; P value not significant) developed significant ST depression at the occasion of the exercise test at either month 3 (n = 3) or month 6 (n = 2). Three of these subjects were immediately treated by coronary balloon dilatation (percutaneous transluminal coronary angioplasty). Thereafter, they participated in a cardiac rehabilitation exercise program for 1 mo and eventually resumed the experimental training program. Within 1 mo after resuming the training program, they reached the same intensity level as before treatment, yet they did not exhibit ST depression in any later exercise test. The two other subjects were instructed to quit the training study and were enrolled in a cardiovascular rehabilitation program after having received the appropriate treatment. Furthermore, during the study, one subject of the CR group was afflicted from overuse trauma at the level of the left shoulder joint. This subject continued to follow the exercise training program except for the weight-lifting
exercises involving shoulder activity. However, after appropriate physiotherapy (6 wk), this subject also resumed the latter part of the training program.

**Cardiorespiratory Measurements**

**Six-month follow-up.** At the start of the study, \( \dot{V}O_2 \), workload, heart rate, and RER at \( V_{\text{slope}} \) threshold (VT) intensity as well as at exhaustion (peak) were similar between groups (Table 1). In PL, 3 and 6 mo of training increased \( \dot{V}O_2 \) at VT intensity by \( \sim 27 \) and 19%, respectively (\( P < 0.05 \)). At peak intensity, corresponding increases in \( \dot{V}O_2 \) were 13 and 16% (\( P < 0.05 \)). Compared with baseline, workload at VT was increased by 16% after 3 mo of training (\( P < 0.05 \)) but not after 6 mo (+3%; not significant). Peak workload was increased by \( \sim 7 \) and 11% at 3 and 6 mo, respectively (\( P < 0.05 \)). \( \dot{V}O_2 \) and workload corresponding with either VT or peak were not significantly different between PL and CR at any time of the study. Furthermore, heart rate and RER at VT and peak were not significantly different between PL and CR after both 3 and 6 mo of training. At baseline, resting diastolic (PL: 84 ± 2 mmHg; CR: 80 ± 2 mmHg) and systolic blood pressures (PL: 139 ± 3 mmHg; CR: 136 ± 3 mmHg) were similar in PL and CR. Compared with PL (138 ± 5 mmHg), 3 mo of training decreased systolic pressure in CR (125 ± 2 mmHg; \( P < 0.05 \)). However, this difference had disappeared by 6 mo of training. Diastolic blood pressure was not different between the experimental groups at any time of the study.

**One-year follow-up.** As shown in Table 1, \( \dot{V}O_2 \), workload, heart rate, and RER values measured at both VT and peak, at 0, 3, and 6 mo of training, were nearly identical in the total groups of subjects (6-mo follow-up) and in the subgroup of subjects who completed the 1-yr follow-up. Compared with baseline, in PL at the end of the 1-yr training period, \( \dot{V}O_2 \)peak was increased by 20% (\( P < 0.05 \)). However, neither \( \dot{V}O_2 \) at VT intensity nor workload at VT and peak at the end of the study were different from baseline values. \( \dot{V}O_2 \), workload, heart rate, and RER at VT and peak were similar between PL and CR at any time of the study. Furthermore, neither the training nor Cr intake per se significantly impacted blood pressure.

**Muscle Force Measurements**

**Six-months follow-up.** At baseline, maximal isometric knee extension force (\( F_{\text{max}} \)) was 143 ± 7 N·m in PL vs. 140 ± 7 N·m in CR (not significant) (Fig. 1). In PL, the training intervention increased \( F_{\text{max}} \) by \( \sim 7\% \) to 153 ± 8 N·m by 3 mo (\( P < 0.05 \)); yet at 6 mo, values had reverted to baseline (146 ± 8 N·m). \( F_{\text{max}} \) values in

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**Table 1. Effect of creatine intake in conjunction with fitness training on cardiorespiratory endurance in men 55–75 yr old**

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<td>VT</td>
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**6-mo follow-up (n = 23)**

**1-yr follow-up (n = 10)**

Values are means ± SE of 23 and 10 observations for the 6-mo and 1-yr follow-up, respectively. A graded maximal cycle ergometer test was performed before (baseline) and after 3, 6, and 12 mo of fitness training combined with either placebo or creatine intake (5 g/day). Oxygen uptake rate (\( \dot{V}O_2 \)), workload, heart rate, and respiratory gas exchange ratio (RER) were determined at the exercise intensity corresponding with the \( V_{\text{slope}} \) threshold (VT) and at the point of volitional exhaustion (peak). *\( P < 0.05 \) compared with the corresponding baseline value. See **METHODS** for further details.
A 2-min rest pause in between. Because power curves consisted of two bouts of 30 maximal contractions with fatigue were measured during an exercise test that was similar to PL at any time of the study. Dynamic torque curves during either bout 1 or 2 were similar between PL and CR at any time of the study.

One-year follow-up. Changes in Fmax during the initial 6 mo of the follow-up mirrored the changes measured in the total group of subjects. However, because of the smaller number of observations, the increase (+4%) in Fmax after 3 mo of training was not statistically significant. Accordingly, Fmax at the end of the study was similar to baseline. Dynamic torque outputs during the dynamic fatigue test were not altered either by the training per se or by CR.

Body Composition

Six-months follow-up. Baseline values for body weight, percent body fat, and fat-free mass were similar between PL and CR (Table 3). Compared with baseline, body weight tended to decrease by 6 mo of training in PL (P = 0.07), whereas it was stable in CR. However, analysis of covariance did not yield a significant treatment effect for body weight. In PL, percent body fat slightly decreased by 6 mo of training (−1.1%, P < 0.05), whereas fat-free mass slightly increased (P < 0.05). Training-induced changes of both percent body fat and fat-free mass were similar between PL and CR.

One-year follow-up. Changes of body weight, percent body fat, and fat-free mass up to 6 mo follow-up paralleled changes observed for the total group of subjects. Compared with baseline, in PL at the end of the study, body weight and fat-free mass were not significantly changed. However, percent body fat was decreased by 1.7% (P < 0.05). There were no significant differences for the body composition measurements between PL and CR at any time of the study.

Muscle Biochemistry and Histochemistry

Six-months follow-up. Muscle Cr, PCr, and TCr content at baseline were similar between PL and CR, yet ATP content was slightly higher in CR (P < 0.05) (Table 4). Furthermore, in PL, values at month 6 were similar to baseline. In CR, compared with baseline, Cr

CR (3 mo: 146 ± 7 N·m; 6 mo 136 ± 8 N·m) were similar to PL at any time of the study. Dynamic force and fatigue were measured during an exercise test that consisted of two bouts of 30 maximal contractions with a 2-min rest pause in between. Because power curves were independent of either training or CR, Table 2 only shows mean dynamic torque outputs per bout. In PL, power output after 3 and 6 mo of training was not significantly different from baseline. Dynamic torque curves during either bout 1 or 2 were similar between PL and CR at any time of the study.

Body Composition

Six-months follow-up. Baseline values for body weight, percent body fat, and fat-free mass were similar between PL and CR (Table 3). Compared with baseline, body weight tended to decrease by 6 mo of training in PL (P = 0.07), whereas it was stable in CR. However, analysis of covariance did not yield a significant treatment effect for body weight. In PL, percent body fat slightly decreased by 6 mo of training (−1.1%, P < 0.05), whereas fat-free mass slightly increased (P < 0.05). Training-induced changes of both percent body fat and fat-free mass were similar between PL and CR.

One-year follow-up. Changes of body weight, percent body fat, and fat-free mass up to 6 mo follow-up paralleled changes observed for the total group of subjects. Compared with baseline, in PL at the end of the study, body weight and fat-free mass were not significantly changed. However, percent body fat was decreased by 1.7% (P < 0.05). There were no significant differences for the body composition measurements between PL and CR at any time of the study.

Muscle Biochemistry and Histochemistry

Six-months follow-up. Muscle Cr, PCr, and TCr content at baseline were similar between PL and CR, yet ATP content was slightly higher in CR (P < 0.05) (Table 4). Furthermore, in PL, values at month 6 were similar to baseline. In CR, compared with baseline, Cr

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One-year follow-up. Changes in Fmax during the initial 6 mo of the follow-up mirrored the changes measured in the total group of subjects. However, because of the smaller number of observations, the increase (+4%) in Fmax after 3 mo of training was not statistically significant. Accordingly, Fmax at the end of the study was similar to baseline. Dynamic torque outputs during the dynamic fatigue test were not altered either by the training per se or by CR.

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Table 3. Effect of creatine intake in conjunction with fitness training on body composition in men 55–75 yr old

<table>
<thead>
<tr>
<th></th>
<th>6 mo follow-up (n = 23)</th>
<th>12 mo follow-up (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Creatine</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>81.3 ± 2.5</td>
<td>79.2 ± 2.3</td>
</tr>
<tr>
<td>Body fat, %</td>
<td>26.1 ± 1.0</td>
<td>25.9 ± 0.9</td>
</tr>
<tr>
<td>Fat-free mass, kg</td>
<td>59.6 ± 1.2</td>
<td>58.4 ± 1.4</td>
</tr>
</tbody>
</table>

Values are means ± SE of 23 and 10 observations for the 6-mo and 1-yr follow-up, respectively. Body composition was assessed by hydrostatic weighing before (baseline) and after 6 and 12 mo of fitness training combined with either placebo or creatine intake (5 g/day). †P < 0.05 compared with the corresponding baseline value.

Table 4. Effect of creatine intake in conjunction with fitness training on muscle biochemistry in men 55–75 yr old

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>6 mo</th>
<th>12 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Creatine</td>
<td>Placebo</td>
</tr>
<tr>
<td>ATP</td>
<td>17.2 ± 0.7</td>
<td>19.7 ± 0.9*</td>
<td>18.0 ± 0.7</td>
</tr>
<tr>
<td>Creatine</td>
<td>45.2 ± 2.4</td>
<td>42.2 ± 1.9</td>
<td>46.5 ± 2.8</td>
</tr>
<tr>
<td>Phosphocreatine</td>
<td>981.1 ± 2.8</td>
<td>1036.8 ± 5.7</td>
<td>930.9 ± 3.6</td>
</tr>
<tr>
<td>Total creatine</td>
<td>143.4 ± 3.1</td>
<td>145.8 ± 6.1</td>
<td>139.5 ± 4.2</td>
</tr>
</tbody>
</table>

Values are means ± SE (mmol/kg dry wt) of 13 (placebo) and 12 (creatine) observations in the 6-mo follow-up vs. 7 (placebo) and 6 (creatine) observations in the 1-yr follow-up. Total creatine was calculated as the sum of creatine and phosphocreatine values. Muscle biopsies were taken from the m. vastus lateralis of the right leg before (baseline) and after 6 and 12 mo of fitness training combined with either low placebo or creatine intake (5 g/day). *P < 0.05, †P = 0.07 compared with the corresponding placebo value. ‡P < 0.05 compared with the corresponding baseline value. See METHODS for further details.

Clinical Chemistry (Data Not Shown)

To investigate the safety profile of long-term Cr intake, routine blood and urine clinical chemistry screening tests were performed during the 6-mo and 1-yr follow-up. All values remained within the normal clinical range throughout the study, with no significant differences between PL and CR. In CR, urinary Cr excretion obviously increased from 0.76 ± 0.12 g/24 h at baseline to 3.46 ± 0.26 g/24 h throughout the 1-yr period of CR. During the course of the 1-yr intervention period, plasma Cr concentration also slightly increased from 1.13 ± 0.02 mg/dl at baseline to 1.24 ± 0.04 mg/dl. Blood lipids were only measured in the 1-yr follow-up group. There were no differences either within or between the groups for total cholesterol, HDL-cholesterol, and LDL-cholesterol at any time of the study. However, at 12 mo of training, compared with PL (141 ± 18 mg/dl), triglycerides were lower (P < 0.05) in CR (88 ± 14 mg/dl).

(+21%, P < 0.05) and TCr (+5%, P = 0.07) increased, whereas PCr and ATP were stable. As shown in Fig. 2, a high negative correlation (r = −0.78, P < 0.05) was found between initial muscle TCr and the increase of muscle TCr produced by 6 mo of CR.

One-year follow-up. Muscle ATP, Cr, PCr, and TCr content at 0 and 6 mo were similar to the values found in the total group of subjects. However, because of the smaller number of observations, changes were not statistically significant. In PL, at the end of the 1-yr follow-up, the relative distribution of type Ia fibers increased by ~40%, whereas type IIX/b number decreased by ~70% (P < 0.05). However, the latter changes were not significantly different from PL.

Compared with baseline, the relative distribution of type IIA fibers increased by ~40%, whereas type IIX/b number decreased by ~70% (P < 0.05). However, the latter changes were not significantly different from PL.

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CREATINE AND AGING

Increasing the level of physical activity is a first-line strategy to improve physical fitness (8). Deterioration of muscle performance capacity due to atrophy can reduce mobility and thus impair the quality of life in older individuals. On the basis of recent observations in young healthy volunteers (27, 34, 48, 50), it was reasonable to assume that CR might stimulate the effects of resistance exercise training on muscle force and power output in the elderly (46). We assessed static and dynamic strength of the knee extensor muscles on an isokinetic dynamometer. The training program, which among other exercises involved weight-lifting exercises for the knee extensors (leg press and leg extension), slightly increased $F_{\text{max}}$ most prominently during the initial stage of the training intervention. Hereafter, $F_{\text{max}}$ surprisingly normalized, despite regular training attendance (~2.5 training sessions/wk) and normal progress of the training intensity. At present, it is unclear why by 6 mo of training the adaptations that had been elicited with 3 mo of training had been lost. Furthermore, Cr intake did not beneficially impact muscle force and power production, either in the total group of subjects (6-mo follow-up) or in the subgroup of subjects completing the full 1-yr training intervention (see Fig. 1). There is evidence from one study (50) to indicate that CR may enhance the effects of a resistance training program on muscle strength by facilitating the progress of training workloads. However, analysis of the training diaries showed that workloads of the weight-lifting exercises were similar between the placebo and CR subjects at any time of the study. Consistent with our present findings, one earlier study, performed by Bermon et al. (7), found no benefit to combining 8 wk of heavy resistance training with Cr intake in older persons. Conversely, two other studies reported improved muscle strength characteristics after either 12 (11) or 14 wk (10) of Cr intake in conjunction with a heavy resistance training program in men >60 yr old (11).

**DISCUSSION**

In this study, we investigated the potential of oral CR to improve physical fitness (8) in older men. Increasing the level of physical activity is a first-line strategy to improve fitness in older people (8, 29, 44). It is known from studies in young volunteers that CR can enhance the beneficial effects of resistance training on muscular functional capacity (48, 50). Therefore, we used CR as a “therapeutic” intervention additive to an exercise training program. Our data show that long-term oral Cr intake at a rate that has been proven to be effective in young subjects, does not enhance physical fitness in older men.

Functional capacity of skeletal musculature is an important component of physical fitness (8). Deterioration of muscle performance capacity due to atrophy can reduce mobility and thus impair the quality of life in older individuals. On the basis of recent observations in young healthy volunteers (27, 34, 48, 50), it was reasonable to assume that CR might stimulate the effects of resistance exercise training on muscle force and power output in the elderly (46). We assessed static and dynamic strength of the knee extensor muscles on an isokinetic dynamometer. The training program, which among other exercises involved weight-lifting exercises for the knee extensors (leg press and leg extension), slightly increased $F_{\text{max}}$ most prominently during the initial stage of the training intervention. Hereafter, $F_{\text{max}}$ surprisingly normalized, despite regular training attendance (~2.5 training sessions/wk) and normal progress of the training intensity. At present, it is unclear why by 6 mo of training the adaptations that had been elicited with 3 mo of training had been lost. Furthermore, Cr intake did not beneficially impact muscle force and power production, either in the total group of subjects (6-mo follow-up) or in the subgroup of subjects completing the full 1-yr training intervention (see Fig. 1). There is evidence from one study (50) to indicate that CR may enhance the effects of a resistance training program on muscle strength by facilitating the progress of training workloads. However, analysis of the training diaries showed that workloads of the weight-lifting exercises were similar between the placebo and CR subjects at any time of the study. Consistent with our present findings, one earlier study, performed by Bermon et al. (7), found no benefit to combining 8 wk of heavy resistance training with Cr intake in older persons. Conversely, two other studies reported improved muscle strength characteristics after either 12 (11) or 14 wk (10) of Cr intake in conjunction with a heavy resistance training program in men >60 yr old (11).

**Table 5. Effect of creatine intake in conjunction with fitness training on muscle histochemistry in men 55–75 yr old**

<table>
<thead>
<tr>
<th>Type</th>
<th>Baseline Mean fiber area, μm²</th>
<th>Placebo</th>
<th>Creatine</th>
<th>6 mo Mean fiber area, μm²</th>
<th>Placebo</th>
<th>Creatine</th>
<th>12 mo Mean fiber area, μm²</th>
<th>Placebo</th>
<th>Creatine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I</td>
<td>3.744 ± 334</td>
<td>4.509 ± 628</td>
<td>4.123 ± 311</td>
<td>4.551 ± 190</td>
<td>4.163 ± 335</td>
<td>4.585 ± 261</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type IIa</td>
<td>3.630 ± 234</td>
<td>4.016 ± 336</td>
<td>4.107 ± 542</td>
<td>4.422 ± 404</td>
<td>4.103 ± 199</td>
<td>4.657 ± 478</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relative area, %</td>
<td>44.0 ± 6.9</td>
<td>55.3 ± 5.4</td>
<td>46.4 ± 6.4</td>
<td>57.2 ± 8.8</td>
<td>45.8 ± 2.7</td>
<td>55.6 ± 6.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type IIa</td>
<td>38.4 ± 7.0</td>
<td>29.0 ± 7.1</td>
<td>38.7 ± 6.2</td>
<td>32.5 ± 7.5</td>
<td>40.1 ± 3.5</td>
<td>40.3 ± 5.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type IIx/b</td>
<td>17.6 ± 3.4</td>
<td>15.0 ± 3.3</td>
<td>14.6 ± 3.3</td>
<td>9.7 ± 6.5</td>
<td>14.0 ± 3.2</td>
<td>5.5 ± 2.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relative number, %</td>
<td>41.8 ± 5.9</td>
<td>52.2 ± 5.5</td>
<td>45.1 ± 5.0</td>
<td>55.3 ± 8.7</td>
<td>44.5 ± 2.1</td>
<td>55.2 ± 5.2</td>
<td></td>
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Values are means ± SE of 7 (placebo) and 6 (creatine) observations. Muscle biopsies were taken from m. vastus lateralis of the right leg before (baseline) and after 6 and 12 mo of fitness training combined with either placebo or creatine intake (5 g/day). *P < 0.05 compared with the corresponding baseline value. See METHODS for further details.
Another factor contributing to physical fitness as well as health is body composition (8). Increased fat-free mass relative to fat mass, by virtue of the high potential of energy turnover in skeletal muscle tissue, can significantly contribute to improved health status. There is evidence from long-term CR studies to indicate that supplementary oral Cr intake in conjunction with resistance training can stimulate muscle hypertrophy (27, 34, 47, 48, 50). Fat-free mass, assessed by hydrostatic weighing, was only marginally increased by the resistance training program used, and there was no additional benefit from the ingestion of Cr (Table 3). Accordingly, fat mass and body weight were not affected by CR. Thus the older subjects enrolled in this study clearly did not exhibit the increase of body weight inherent to CR in samples of young subjects (26, 30, 47). In fact, the failure of CR to increase fat-free mass probably also largely explains the unchanged $F_{\text{max}}$.

Functional capacity of the cardiorespiratory system also is an important factor contributing to physical fitness. We evaluated cardiorespiratory fitness by means of a maximal exercise test on a bicycle ergometer. In fact, there is no clear rationale from literature data to anticipate that CR might enhance endurance exercise capacity (26, 30, 47). However, because the ability to cope with high workloads in cycling in older individuals is often limited by peripheral muscle weakness rather than by cardiorespiratory factors (2), we assumed that CR in this population might enhance cycle performance in both training and testing. However, training workloads were identical between groups from the start to the end of the study. Furthermore, indexes of submaximal and maximal endurance exercise performance during the maximal exercise test were significantly improved by the training intervention, yet were independent of CR.

Our present findings clearly indicate that the potential of CR to enhance muscular functional capacity, which is explicit in samples of young healthy volunteers (26, 30, 47, 48), is absent in the population of men between 55 and 75 yr of age studied here. Two obvious arguments can be cited to explain the apparently differential response of younger and older individuals to CR. First, it is well established that low initial muscle Cr content predisposes to good responsiveness to CR (24, 25). In the present study, we showed a similar relationship also to exist in older individuals: CR produced the largest increase of muscle TCr content in these subjects with the lowest initial values (see Fig. 2). However, because mean initial TCr contents were substantially higher [140–145 mmol/kg dry wt (dw)] than common values for young healthy subjects (115–125 mmol/kg dw) (24, 25), the increases of muscle Cr content due to supplementation on the average were very small. Similar findings were reported by Rawson et al. (41), who found muscle PCR content to be ~20% higher and the response to acute CR to be smaller in old (70 ± 3 yr) compared with young (24 ± 1 yr) subjects. However, it is important to note that the duration of the present intervention trial (1 yr) was substantially longer than any earlier CR study in either young volunteers (27, 48) or older subjects (7, 10, 11, 42). In this respect, there are some data to suggest that the effects of short-term Cr intake may fade on long-term supplementation (13, 27, 48, 50). We thus cannot exclude that Cr ingestion produced some beneficial effects on muscle performance capacity during the initial stage of the intervention, which then disappeared by 6 mo of training. Two studies found 7 days (23) and 8 wk (11) of CR to cause a small increase of dynamic and isometric muscle force in elderly subjects. Accordingly, Brose et al. (10) recently demonstrated that, compared with placebo, CR in conjunction with 14 wk of heavy resistance training increased fat-free mass and isometric knee extension torque in male subjects by ~3 and 25%, respectively. However, these investigators also reported that the gain in isometric ankle dorsiflexion torque in female subjects after combined Cr intake and resistance training was smaller compared with their placebo counterparts.

Some (1, 17), but not all (49), studies have reported CR in combination with resistance training to have a cholesterol-lowering effect. In this study in older individuals, we could not demonstrate a beneficial effect of supplementary Cr intake on either blood total cholesterol or on the HDL- and LDL-cholesterol fractions measured by routine clinical screening tests. Cholesterol levels were stable in either experimental group throughout the study, which also indicates that the exercise training-program per se did not alter blood lipid profile. This is probably explained by the fact that the training volume did not meet the threshold to decrease blood lipids (15, 16).

Long-term data with regard to potential adverse side effects of CR are very scarce. With the exception of two negative case reports in patients with preexisting renal disease (33, 40) and one study in Sprague-Dawley rats serving as a model for cystic renal disease (18), data to prove that CR per se could harm renal function in healthy individuals are entirely lacking (38, 39). In the present study, Cr intake at a rate of 5 g/day for 1 yr did not alter urinary albumin excretion. Furthermore, Cr ingestion produced a small, yet insignificant, increase of plasma Cr concentration in the early stage of the intervention period, but no further increase was observed from month 3 to month 12 of the study. However, four subjects of the Cr group vs. only one in the placebo group ($\chi^2$ test; not significant) developed ST depression during ECG stress testing during phase I of the intervention. Although the incidence of ST depression was not statistically significant between the experimental groups, this issue deserves particular attention in future studies, in particular in subjects at risk of or afflicted by cardiovascular disease.

It may be argued that CR did not enhance muscular functional capacity because the resistance training workloads used (20–30 RM) were too low. Indeed, it is clearly established that high workloads (5–10 RM) are needed for resistance training to produce muscle hypertrophy in older individuals (20, 21). Therefore, we cannot exclude that older persons involved in heavy
resistance training, in contrast with the moderate resistance plus cardiorespiratory training program used in the present study, still might benefit from Cr intake. However, only a marginal fraction of the older population is involved in heavy resistance training. In fact, the training volume and intensity used in this study even largely exceed the level of physical activity typical to the vast majority of the sedentary Western older population, and there is no evidence from literature data that long-term CR alone, in the absence of exercise training, can beneficially impact neuromuscular performance capacity. In addition, the potential of exercise training programs to improve performance-related measures of functional capacity in older individuals as a rule is small (32), which is in keeping with our present observations.

In conclusion, the present study clearly shows that CR at a rate of 5 g/day is not an effective intervention to enhance physical fitness in men 55–75 yr of age enrolled in an exercise training program involving both endurance exercise and moderate resistance training.

The authors thank Monique Ramaekers and Hilde Verbiest for providing skilled technical assistance.

DISCLOSURES

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