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Journal of Applied Physiology 94:651-659, 2003. First published Oct 25, 2002;
doi:10.1152/japplphysiol.00755.2002

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Effect of dietary supplements on lean mass and strength gains with resistance exercise: a meta-analysis

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Submitted 15 August 2002; accepted in final form 14 October 2002

Nissen, Steven L., and Rick L. Sharp. Effect of dietary supplements on lean mass and strength gains with resistance exercise: a meta-analysis. *J Appl Physiol* 94: 651–659, 2003. First published October 25, 2002; 10.1152/japplphysiol.00755.2002.—The purpose of this study was to quantify which dietary supplements augment lean mass and strength gains during resistance training. Peer-reviewed studies between the years 1967 and 2001 were included in the analysis if they met a predetermined set of experimental criteria, among which were at least 3-wk duration and resistance-training 2 or more times a week. Lean mass and strength were normalized for meta-analysis by conversion to percent change per week and by calculating the effect size for each variable. Of the 250 supplements examined, only 6 had more than 2 studies that met the criteria for inclusion in the meta-analysis. Creatine and β-hydroxy-β-methylbutyrate (HMB) were found to significantly increase net lean mass gains of 0.36 and 0.28%/wk and strength gains of 1.09 and 1.40%/wk ($P < 0.05$), respectively. Chromium, dehydroepiandrosterone, androstenedione, and protein did not significantly affect lean gain or strength. In conclusion, two supplements, creatine and HMB, have data supporting their use to augment lean mass and strength gains with resistance training.

creatine; β-hydroxy-β-methylbutyrate; muscle mass; resistance training

IT SEEMS INTUITIVE THAT additional nutrients may be necessary during intense resistance exercise to allow for maximal "expression" of muscle and strength gains. The use of general and specific dietary supplementation is widespread among both serious and casual athletes with several hundred specific formulas being marketed. The scientific support for specific "hyper" nutrition as an adjunct for muscle growth has been assessed periodically in the form of reviews (18, 27, 38). Although this traditional narrative is well accepted, it is usually nonquantitative and often unsystematic, and conclusions are often open to subjectivity (47). This has led to confusion in the literature on what specific and general nutrition is of value for numerous conditions, including augmentation of the effects of exercise on muscle mass and strength.

A more robust and quantitative approach to the problem has been proposed in the form of a meta-analysis of the data. This technique minimizes subjectivity by standardizing selections, data pooling, and data analysis to draw conclusions. Although the meta-analytical approach offers a more standardized and nonbiased method of data analysis, as with a traditional review, it is still confined to the assessment of research available at the time of writing and is still subject to biases such as negative studies, which are often not published.

The primary objective of the present meta-analysis was to determine whether supplementation of dietary components, above normal intakes or above the requirement, augment lean mass gains associated with resistance training above that of the appropriate control treatment. A secondary objective was to determine whether dietary supplementation during resistance training could augment strength gains.

METHODS

Data Sources

Supplements. For the purposes of this study, the use of the term "supplement" means any oral product designed to augment the effects of resistance-training exercise. A list of substances was compiled from the product lists of eight dietary-supplement marketing companies, a review of six magazines targeted specifically at the body-building community, and five published scientific reviews on dietary supplements (18, 27, 38, 45, 56). The compiled list contained about 250 supplements and was used to search the literature.

Initial database screening. The search for literature was limited to English language citations published between 1967 and 2001, which is the time period covered by the PubMed database. MeSH[1] terms body composition, anthropometry, exercise, and human were then combined with the text words supplement (truncated) and the desired supplement name. The results were then confined to clinical trials

[1]MeSH terms are the National Library of Medicine's controlled vocabulary used for indexing articles in PubMed. MeSH terminology provides a constant way to retrieve information that may use different terminology for the same concept.

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only. Where Greek symbols were present in a supplement's name, the symbols were omitted in the search terms. For example, β-hydroxy-β-methylbutyrate (HMB) was changed to the search term "hydroxy and methylbutyrate."

A title scan of each PubMed database hit was then carried out. Titles were rejected if they indicated that the study did not involve a dietary supplement, clearly did not involve any form of resistance exercise, or the subjects suffered from an abnormal health condition.

A hand search was made of certain relevant peer-reviewed journals, which were not indexed by PubMed. In addition, the reference sections of two review papers that focused on anabolic supplements (20, 38) were analyzed in a similar manner. The titles of the indexed references were then selected or rejected in accordance with the title scan mentioned previously.

The abstracts of the preliminary citations were then examined for the following criteria: *1*) studies had to be published in English; *2*) full-body resistance training had to have been carried out two or more times a week; *3*) a placebo control had to have been administered; *4*) the study had to have been at least 3 wk in duration; and *5*) an estimate of lean body mass had to be made. If any of these criteria were unclear on analysis of the title or abstract, the full text article was examined. Citations were rejected if they were found to be a thesis, an abstract, a roundtable discussion, a letter, or a comment.

Study Inclusion/Exclusion

Subject. Only studies using healthy adults (>18 yr of age) were included for analysis. There was no discrimination of gender, and no restrictions were placed as to the exercise history of the subjects, although training was recorded as a variable.

Experimental design. Only randomized, placebo-controlled studies published in peer review journals were selected. Non-double-blinded protocols were included because of the rarity in which the subjects and researchers were questioned posttreatment to ascertain whether in fact the double-blind protocol was successful (52). Studies were excluded if there was any dietary restriction imposed that could compromise the hypertrophic consequences of the resistance exercise. The study had to be at least 3 wk in duration and had to involve subjects carrying out a full-body (all major muscle groups) resistance-training regimen two or more times per week. Studies were included regardless of statistical significance of the results. If more than one independent study (conducted at different times) was included in a paper, each study met the inclusion criteria, and/or separate data were presented, each was counted as a separate study. Final selection of supplements depended on having at least two studies that met all the inclusion criteria. Supplements that had only one study were not included because of the inability to conduct further statistical analysis on the data set.

Supplement. Only substances that were consumed in excess of the daily requirement (if established) were included. Studies that purposefully created a deficiency of a nutrient and then added that nutrient back to the diet during the trial were not included in this meta-analysis. To be included, the supplement (and placebo) had to be administered daily by mouth throughout the treatment period. The exception to this was in dehydroepiandrosterone (DHEA), where the manufacturers recommend that a 2-wk-on, 1-wk-off cyclic regimen was adhered to. Studies were excluded if the supplement was given in combination with any other potentially anabolic substance. In studies where more than one dosage was used, the dosage closest to the mean of that used in other studies involving the supplement was used. For creatine, the usual dosage included a loading dosage (10–25 g/day for 3–7 days) followed by a constant dose of 2–10.5 g/day. In addition, where there was more than one form of the same supplement used (such as creatine monohydrate and creatine phosphate or chromium picolinate and chromium chloride), the supplement form more frequently used in other studies was chosen.

Feeding studies involving protein are problematic because they are difficult to blind and a single placebo is impossible to design. However, it was decided to evaluate protein as a supplement in this meta-analysis but under slightly more relaxed criteria for two reasons. First, these products are the most extensively used supplements on the market, and second, based on the difficulties involved, there may never be definitive data generated on the potential of protein supplementation to augment the effects of resistance training. Because subjects usually knew whether they were receiving the protein treatment, the chances of a positive "placebo effect" were greatly increased. The placebo-controlled requirement for inclusion was not used in searching protein studies. In addition, studies were included where protein was combined with other conventional nutrients.

Outcome measures. The primary outcome criteria was that of lean body mass. Estimates of lean mass could be in the form of lean body mass, fat-free mass/weight, fat and bone-free mass, or provided data necessary to calculate one of these variables. Any physical measure of body composition was accepted as long as the same method was used to obtain values before and after the treatment period. In studies where the body composition data were presented in graphic form only, an attempt was made to contact the author and acquire the original data for more accurate inclusion in the meta-analysis. Where the data were unattainable, an estimate was made from the graphic form of data presentation.

Strength was the secondary outcome criterion, but papers were not rejected if they failed to report strength data. Strength data were standardized within a study by averaging the percent change for all reported strength measures.

Data Extraction

Information collected. Each of the studies that met the inclusion criteria was recorded on a coding sheet. The following characteristics of each study were recorded: author(s), publication year, originating journal, study title, where the study was found (PubMed, cross-referenced, or hand searched), supplement involved, supplement dose, substance used as placebo, administration method, subjects in the treatment group, subjects in the placebo group, dietary control/analysis, subject exercise history, resistance exercise load (h/wk), short description of the resistance training protocol, subject gender, subject average age or age range, body composition measurement method, body composition variable, study duration, and treatment and placebo pre- and postvalues for lean mass and strength. Where necessary, means and standard deviations were approximated from figures contained in the actual manuscript, and in studies were mean values were not presented with standard errors or deviations, the standard deviations were estimated from calculations based on variability from other studies included in the meta-analysis.

Quality scoring. The quality of the papers included in the final analysis were subjected to a quality assessment instrument developed by Chalmers et al. (15) and Rochon et al. (58). This instrument scores studies on their reported com-

pliance with a set of 14 aspects of study methodology, among which included (points possible to award) *1*) control appearance or regimen (3 or 0), *2*) randomization blinding: was it blind? (10, 5, or 0), *3*) patients blinded (8, 4, or 0), *4*) observers blinded to treatment (8, 4, or 0), *5*) observers blinded to results (10, 5, or 0), *6*) previous estimate of numbers (3 or 0), *7*) testing compliance (3, 1.5, or 0), *8*) results of randomization on pretreatment variables and inclusion analysis (3, 1.5, or 0), *9*) major end points (4, 1, or 0), *10*) post-β estimate (negative trials only; 3, 1.5 or 0), *11*) confidence limits (3, 1.5, or 0), *12*) statistical analysis (4, 2, 1, or 0), *13*) withdrawals after randomization (3, 1.5 or 0), and *14*) side effects discussion (3, 1.5 or 0). Each assessor was then given copies of all studies and instructed to assess them without revealing or discussing any scores with each other. The potential scores derived from the assessment procedure range from 0 to 74 for "trials in which all differences measured are statistically significant" and 0 to 68 for studies in which "the difference between the compared treatments is not statistically significant" (58). To maximize assessment consistency, the two assessors discussed any discrepancies regarding the interpretation of the 14 aspects before assessment. The assessment results are presented as a percentage of the maximal score in each case. Previous use of this assessment procedure assessing 242 published journal articles found a mean score of 38.5 ± 13.1% (58).

Statistical analysis. The major objective of this study was to quantify the effect of dietary supplements on lean mass and strength. This was accomplished in two ways. Gains in strength and lean mass were converted to percent gain per week for both treatment and placebo groups. This, in effect, corrected for starting values of lean mass, time of the experiment, and indirectly for gender and age, because lean mass is related to both of these factors. The percentage gains were then analyzed by using ANOVA with main effects of study group (treatment or placebo) and supplement used.

Effect size calculation. A second method of data standardization was the calculation of an effect size (ES) for each study. The ES of lean mass and strength gains were calculated in accordance with the method outlined by Glass in 1977 (25) as follows

$$ES_{pre} = (X_{pre} - Y_{pre})/SD(Y_{pre})$$

$$ES_{post} = (X_{post} - Y_{post})/SD(Y_{post})$$

where pre is mean value for variable before treatment, post is mean value for variable after treatment period, X is treatment group mean, Y is placebo group mean, and SD is standard deviation.

The difference between the pre- and posttrial ES was then calculated to obtain the ES of the dietary supplements' effect on lean mass and strength. An ES is defined as a unitless measure of the efficacy of each supplement centered at zero if the supplement effect is no different than that of the placebo. A scale for ES has been suggested by Cohen (19), with 0.8 reflecting a large effect, 0.5 a moderate effect, and 0.2 a small effect.

The resulting pre- and poststudy ES achieved for each study were analyzed by using analysis of covariance to determine whether correction of the posttrial ES in accordance with study duration was necessary. The analysis yielded no significant effect, and a correction of the posttrial ES with study duration was not performed.

In an attempt to reduce potential bias, each calculated ES was multiplied by a correction factor defined by Hedges and Olkin (32) that adjusts values depending on the originating study's sample size. In no case did the bias correction approach significance, so the corrected values were not presented in the results.

ES for each supplement was tested for homogeneity by using the equation proposed by Hedges (31) and Rosenthal and Rubin (59). In all cases, there was no indication that samples were nonhomogeneous (data not shown).

Finally, to analyze for the possibility of bias among our sample of clinical trials, funnel plots were constructed for each supplement. This involved plotting ES on the horizontal axis and the number of trials on the vertical axis. Funnel plot asymmetry suggests bias; however, no bias was found for any of the supplements tested (data not shown).

The pooled ES were analyzed by using a one-way ANOVA with main effects of the supplement used. A second analysis was conducted to determine whether ES differed from zero. Statistical analysis was performed by using the general linear models of SAS (60). Results were considered significant if $P \leq 0.05$ was obtained. Confidence intervals (CI) were in all cases reported at the 95% level.

RESULTS

Included Studies

Of the ~250 candidate supplements, only 48 studies (in 40 citations) met all the inclusion criteria. Of these, six supplements were supported by greater than one citation each; creatine (n = 18), HMB (n = 9), chromium (n = 12), DHEA (n = 2), androstenedione (n = 3), and protein (n = 4, with relaxed inclusion criteria). Characteristics of the included studies are summarized in Table 1. Seven other supplements met the inclusion criteria but were supported by only one study (1, 2, 9, 21, 22, 63). Of the single-study supplements, amino acids, androstenediol, boron, and bovine colostrum all had positive but not significant results, whereas pyruvate, tribulus terrestris, and vanadyl sulfate had negative but not significant results. In addition, three citations, two involving creatine and one involving chromium picolinate, were excluded because they were found to be duplicates of previously published (and included) studies (12, 28, 66). Two citations were found for boron, but it was determined that they were in fact the same study (22, 26).

Of the 40 citations that met all the inclusion criteria, 7 citations reported two independent studies, 3 citations examined the independent effect of two different supplements (34, 49, 71), 3 citations involved a single supplement in separate experiments on men and women (30, 33, 53), 1 study examined the effects of supplementation on both trained and untrained subjects (5), and 1 citation depicted two independent studies that both met the inclusion criteria (49). In the studies where body composition was measured by using both hydrostatic weighing and skinfold measurements (7, 53, 63), the hydrostatic weighing values were used as the method of choice (8). Of the 48 studies, percent change in strength could not be calculated for 2 of the creatine, 2 of the chromium, and 1 of the protein studies. Lean ES could not be calculated for three of the creatine studies and one of the chromium studies. Strength ES could not be calculated for three of the creatine, two of the chromium, and one of each of the DHEA, androstenedione, and protein studies.

Table 1. *Summary of characteristics of all studies meeting the inclusion criteria*

Authors	Year	Journal	Treatment, *n*	Placebo, *n*	Gender	Dosage/Day	Age	Training Status	Training, h/wk	Duration, wk	Body Composition	Quality Score, %
						Creatine						
Arciero et al. (3)	2001	*Metabolism*	10	10	M	20 g/day-5 days: 10 g	21.0	U	3	4	DEXA	38.1
Bemben et al. (4)	2001	*Med Sci Sports Exerc*	9	8	M	20 g/day-5 days: 5 g	19.2	T	4	9	HW	8.5
Bermon et al. (5)	1998	*Acta Phys Scand*	8	8	Both	20 g/day-5 days: 7 g		U	3	8	SF	32.4
Bermon et al. (5)	1998	*Acta Phys Scand*	8	8	Both	20 g/day-5 days: 7 g		T	3	8	SF	32.4
Brenner et al. (7)	2000	*J Str Cond Res*	7	9	F	10 g/day-7 days: 2 g	18–22	T	3	5	HW	40.0
Chrusch et al. (16)	2001	*Med Sci Sports Exerc*	16	14	M	0.3 g/k-5 days: 0.07 g/k	70.7	U	3	12	DEXA	43.9
Jowko et al. (34)	2001	*Nutrition*	11	10	M	20 g/day-7 days: 10 g	19–23	U	3	3	BIA	38.9
Kelly et al. (35)	1998	*J Str Cond Res*	9	9	M	20 g/day-4 days: 5 g	26.5	T	4	4	SF	33.5
Kirksey et al. (37)	1999	*J Str Cond Res*	15	21	Both	0.3 g/kg	19.9	T	3	6	HW	51.2
Kreider et al. (40)	1998	*Med Sci Sports Exerc*	11	14	M	15.75 g	19.9	T	4	4	DEXA	55.8
Larson-Meyer et al. (41)	2000	*J Str Cond Res*	7	5	F	17 g/day-7 days: 5 g		T	2	13	DEXA	40.4
Noonan et al (51)	1998	*J Str Cond Res*	13	13	M	0.1g/kg	18–23	T	4	8	HW	41.6
Pearson et al. (55)	1999	*J Str Cond Res*	8	8	M	5 g	20.7	T	4	10	SF	31.2
Peeters et al. (57)	1999	*J Str Cond Res*	11	14	M	20 g/day-3 days: 10 g	19–29	T	4	6	SF	31.2
Stone et al. (63)	1999	*Int J Sports Nutr*	9	11	M	0.22 g/kg	18.4	T	3	5	HW	28.1
Stout et al. (64)	1999	*Nutr Res*	8	8	M	21 g/day-4 days: 10.5 g	19.6	T	4	8	DEXA	23.1
Vandenberghe et al. (65)	1997	*J Appl Phys*	10	9	F	20 g/day-4 days: 5 g	19–22	U	3	10	HW	30.8
Volek et al. (67)	1999	*Med Sci Sports Exerc*	10	9	M	25 g/day-7 days: 5 g	25.5	T	4	12	HW	50.4
Average			10.0	10.4			24.0		3.4	7.5		36.4
						HMB						
Gallagher et al. (23)	2000	*Med Sci Sports Exerc*	12	14	M	38 mg/kg	21.7	U	3	8	SF	37.7
Jowko et al. (34)	2001	*Nutrition*	9	10	M	3 g	19–23	U	3	3	HW	38.9
Kreider et al. (39)	1999	*Int J Sports Med*	13	15	M	3 g	25.1	T	3	4	DEXA	43.4
Nissen et al. (short) (49)	1996	*J Appl Phys*	15	6	M	3 g	19–22	U	3	3	TOBC	25.8
Nissen et al. (long) (49)	1996	*J Appl Phys*	13	15	M	3 g	19–29	T	4	7	TOBC	16.5
Panton et al. (men) (53)	2000	*Nutrition*	21	18	M	3 g	24.0	Both	3	4	HW	39.0
Panton et al. (wom) (53)	2000	*Nutrition*	18	18	F	3 g	27.0	Both	3	4	HW	39.0
Slater et al. (62)	2001	*Int J Sport Nutr*	9	9	M	3 g		T	3	6	DEXA	40.5
Vukovich et al. (69)	2001	*J Nutr*	14	17	Both	3 g	70.1	U	2	8	DEXA	33.5
Average			13.8	13.6			29.2		3.0	5.2		34.9
						Chromium						
Boyd et al. (6)	1998	*J Nutr Biochem*	13	9	Both	1,000 μg		T	2	13	SF	33.5
Campbell et al. (14)	1999	*J Appl Phys*	9	9	M	924 μg	50–75	U	2	12	HW	36.1
Clancy et al. (17)	1994	*Int J Sports Nutr*	18	18	M	200 μg	19.4	T	4	9	HW	25.4
Hallmark et al. (29)	1996	*Med Sci Sports Exerc*	8	8	M	200 μg	24.0	U	3	12	HW	32.4
Hasten et al. (30)	1992	*Int J Sports Nutr*	18	19	M	200 μg		U	3	12	SF	26.5
Hasten et al. (30)	1992	*Int J Sports Nutr*	12	10	F	200 μg		U	3	12	SF	26.3
Joseph et al. (33)	1999	*Metabolism*	9	8	M	924 μg	63	U	2	12	HW	39.1
Joseph et al. (33)	1999	*Metabolism*	8	7	F	924 μg		U	2	12	HW	39.4
Livolsi et al. (43)	2001	*J Str Cond Res*	8	7	F	500 μg	19–29	T	3	6	HW	37.5
Lukaski et al. (44)	1996	*Am J Clin Nutr*	12	12	M	200 μg	19.6	U	4	8	DEXA	28.7
Volpe et al. (68)	2001	*J Am Coll Nutr*	22	22	F	400 μg		U	2	12	HW	37.5
Walker et al. (70)	1998	*Med Sci Sports Exerc*	7	7	M	3.5 μmol	20.2	T	4	14	HW	36.4
Average			12.0	11.3			34.0		2.8	11.2		33.2

Continued

Table 1. —*Continued*

Authors	Year	Journal	Treatment, *n*	Placebo, *n*	Gender	Dosage/Day	Age	Training Status	Training, h/wk	Duration, wk	Body Composition	Quality Score, %
						Androstenedione						
Broeder et al. (9)	2000	*Arch Intern Med*	15	18	M	200 mg	48.1		3	12	DEXA	34.9
King et al. (36)	1999	*JAMA*	10	10	M	300 mg; 2-on, 1-off	45.0	U	3	8	HW	37.1
Wallace et al. (71)	1999	*Med Sci Sports Exerc*	20	10	M	100 mg	19–29	T	3	12	HW	24.7
Average			15.0	12.7			39.0		3.0	10.7		32.2
						Dehydroepiandrosterone						
Brown et al. (10)	1999	*J Appl Phys*	9	10	M	150 mg; 2-on, 1-off	48.1	U	3	8	HW	24.3
Wallace et al. (71)	1999	*Med Sci Sports Exerc*	10	10	M	100 mg	19–29	T	N/A	12	HW	24.7
Average			9.5	10.0			36.1		3.0	10.0		24.5
						Protein						
Burke et al. (11)	2001	*Int J Sport Nutr*	10	5	M	1.20 g/kg	18–31	T	5.5	6	DEXA	33.8
Campbell et al. (13)	1995	*Am J Phys*	6	6	Both	0.80 g/kg	56–80	U	3	12	HW	27.2
Lemon et al. (42)	1992	*J Appl Phys*	12	12	M	1.27 g/kg	22.4	U	5.5	4	HW	21.3
Nissen et al. (short) (49)	1996	*J Appl Phys*	6	7	M	1.35 g/kg	19–29	U	3	3	TOBC	25.8
Average			8.5	7.5			34.7		4.3	6.3		27.0

Dosages are given in daily dosages. For creatine, first dosage is loading and second is maintenance. Dehydroepiandrosterone 2-on, 1-off dose was cycled "on" (taken) for 2 wk and then "off" (not taken) for wk; U, untrained (no previous resistance training in the last 3 mo); T, trained (undergoing some form of resistance training before study); DEXA, duel-energy X-ray absorptiometry; HW, hydrostatic weighing; SF, skinfold thickness; TOBC, total body electrical conductivity; M, male; F, female; N/A, not applicable.

Creatine

Eighteen studies met the inclusion criteria for creatine, with the average quality score being 36.4%. The studies were largely published in exercise-related journals between 1997 and 2001. The studies averaged 7.5 wk in duration. The average loading dose was 19.4 g/day for 5.3 days. The average maintenance dose was 6.7 g/day. Overall, creatine supplementation resulted in a net gain in lean mass (placebo treatment) of 0.36%/wk (Fig. 1*A*; CI: 0.25–0.48%, $P < 0.001$). Expressing the data as an ES indicated a net lean mass gain of 0.26 (Fig. 1*B*; CI: 0.17–0.34%, $P < 0.001$). It should be noted that the gain in strength for the placebo group was significantly different from zero but approximately one-half that of placebo groups for the other supplements (Fig. 2*A*). Creatine supplementation resulted in a significant net strength gain of 1.09%/wk (Fig. 2*A*; CI: 0.65–1.52%, $P < 0.001$). ES for net strength gain was 0.36 (Fig. 2*B*, CI: 0.28–0.43%, $P < 0.001$).

HMB

A total of nine studies that involved HMB supplementation qualified for analysis, with the average quality score being 34.9%. All studies involved supplementation of HMB at 3 g/day (or equivalent) and resulted in a net increase in lean mass gain of 0.28%/wk (Fig. 1*A*; CI: 0.13–0.42%, $P < 0.001$). As with creatine,

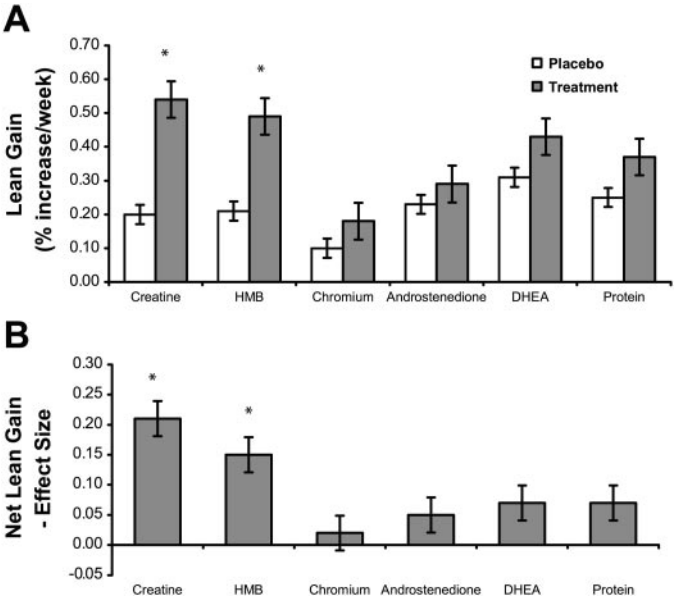

Fig. 1. Comparison of the net lean mass gain of the placebo and treatment groups for each supplement. *A*: lean gain as percent gained per week. *B*: net effect size for each supplement. HMB, β-hydroxyl-β-methylbutyrate; DHEA, dehydroepiandrosterone. *Significant effect of the treatment vs. the placebo ($P < 0.05$).

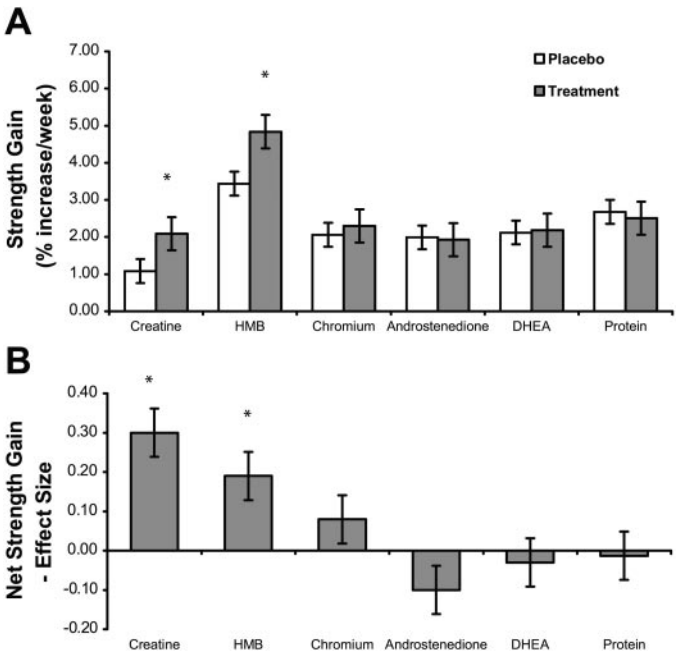

Fig. 2. Comparison of the net strength gain of the placebo and treatment groups for each supplement. *A*: strength gain as percent gained per week. *B*: net effect size for each supplement. *Significant effect of the treatment vs. the placebo ($P < 0.05$).

HMB supplementation resulted in a significant ES of a net lean mass gain of 0.15 (Fig. 1*B*; CI: 0.06–0.24, $P < 0.005$). Strength gains for the HMB placebo and treatment groups are presented in Fig. 2. When expressed as percent gain per week, HMB caused a net increase of 1.40%/wk (CI: 0.41–2.39%, $P < 0.01$). The ES of net strength gain was 0.19 for HMB (CI: 0.09–0.29, $P < 0.01$).

Chromium

Twelve studies were found that involved chromium supplementation with weight training. Chromium supplementation caused a small, nonsignificant increase in net lean mass gain of 0.08%/wk (Fig. 1*A*; CI: −0.05–0.21%, $P = 0.22$) and a nonsignificant strength gain of 0.25%/wk (Fig. 2*A*; CI: −0.31–0.80%, $P = 0.41$). The net lean mass gain ES was 0.02 (Fig. 1*B*; CI: −0.07–0.11, $P = 0.66$), and the net change in strength gain ES was 0.08 (Fig. 2*B*; CI: −0.14–0.30, $P = 0.47$). The quality of the studies involved with chromium averaged 33.2%.

Androstenedione and DHEA

Of the collected studies, three concerned androstenedione and two were on DHEA. Androstenedione and DHEA both failed to significantly affect lean mass or strength gains with resistance training (Figs. 1 and 2). Androstenedione supplementation resulted in gains in lean mass of 0.05%/wk (Fig. 1*A*; CI: −0.20–0.31% $P = 0.68$) and strength loss of −0.06%/wk (Fig. 2*A*; CI: −1.28–1.16%, $P = 0.92$) with corresponding ES of 0.05 (Fig. 1*B*; CI: −0.11–0.21, $P = 0.55$) and −0.10 (Fig. 2*B*; CI: −0.50–0.31, $P = 0.65$), respectively. DHEA supplementation resulted in a lean mass gain of 0.12%/wk (Fig. 1*A*; CI: −0.19–0.43%, $P = 0.46$) and a strength gain of 0.06%/wk (Fig. 2*A*; CI: −1.44–1.55%, $P = 0.94$) with a corresponding ES of 0.07 (Fig. 1*B*; CI: −0.13–0.27, $P = 0.49$) for lean mass and −0.03 (Fig. 2*B*; CI: −0.60–0.54, $P = 0.92$) for strength gain. The quality of the studies with both DHEA and androstenedione averaged 24.5 and 32.2%, respectively.

Protein

Four studies were found that involved protein supplementation with resistance training (11, 13, 42, 49). Both lean mass and strength gain were unaffected by protein supplementation, although treatments were not blinded and inadequate placebos were used in these studies. Protein supplementation resulted in a nonsignificant increase in net lean mass gain of 0.12%/wk (Fig. 1*A*; CI: −0.07–0.31%, $P = 0.31$) and decrease in net strength gain of −0.18%/wk (Fig. 2*A*; CI: −0.87–0.51%, $P = 0.66$). Statistical interpretation of the data did not change when data were expressed as ES; the net lean mass gain ES was 0.07 (Fig. 1*B*; CI: −0.03 - 0.17, $P = 0.25$), and the net change in strength gain ES was −0.01 (Fig. 2*B*; CI: −0.15–0.13, $P = 0.87$). The quality scoring of the protein supplementation studies was generally low because of the lack of complete blinding and averaged 27.0%.

Influence of Subject Training Status

An analysis of the differences in strength gains achieved in the trained and untrained placebo groups from all included studies was performed to determine whether training status biased either lean mass or strength gains. Lean mass gain was unaffected by training status. However, analysis showed that previously untrained subjects gained more strength with resistance training than pretrained subjects (2.62%/wk; CI: 2.07–3.17 vs. 0.90%/wk, CI: 0.42–1.39%, $P < 0.01$, respectively).

DISCUSSION

Of the original list of ~250 substances marketed as dietary supplements, creatine and HMB were the only supplements found to be effective in augmenting lean tissue gain with resistance training. Findings from this meta-analysis are consistent with most previous review papers that conclude that creatine is effective in increasing lean mass and strength gains (18, 38, 45). However, most of the papers on HMB have been published in the last 2 yr, thus making most reviews, to date, limited.

Several supplements were excluded from this meta-analysis because of the necessity of multiple publications (minimum of two). Among those excluded, none reported significant positive effects in augmenting lean tissue gain with their use. However, further studies are needed to draw definitive conclusions on those dietary supplements with the limited research to date.

With regard to lean gain, creatine and HMB have similar effects, with lean gain approximately doubling

over the placebo group. Although this could suggest a similar mechanism of action, the literature would suggest independent mechanisms. There are different theories for the mechanism of action for creatine. Willoughby and Rosene (72) reported an increase in muscle strength and size as a result of increased myosin heavy chain expression, whereas Parise et al. (54) concluded that creatine supplementation may have anticatabolic action in some proteins. Both of these observations seem to fit with the general hypothesis that creatine acts by enhancing cell volume, which in turn is a stimulus for protein synthesis (18). HMB, on the other hand, appears to act by either decreasing cellular protein breakdown or by providing structural precursors for membrane cholesterol synthesis and, thereby, affecting cell integrity (50). In addition, one study (34) has also shown that HMB and creatine are roughly additive in nature, again suggesting separate mechanisms of action.

As mentioned in *Study Inclusion/Exclusion*, analysis of protein supplementation is potentially complicated by the lack of placebo blinding and the numerous confounding effects of defining protein levels as well as added nutrients to the protein supplement. However, even with the potential to create false positive data, there was no effect of protein supplementation on lean mass and strength gains. It should be noted that in all the studies, the control diet had or likely had protein intakes above the current RDA of 0.8 $g \cdot kg^{-1} \cdot day^{-1}$. Therefore, the referenced studies are not an indication of a requirement. However, the data do clearly indicate there is not an effect of excess protein intake on lean mass or strength gains with resistance training.

The safety of creatine and HMB supplements has been addressed in several papers. Creatine data suggest that supplementation does not result in adverse health effects (61), whereas HMB supplementation during resistance training (study length ranged from 3 to 8 wk) had no adverse affects on hematology, or hepatic or renal function (24, 48). However, HMB supplementation did result in a net decrease in total cholesterol, low-density lipoprotein cholesterol, and systolic blood pressure (48).

Limitations

This study, like others, is prone to certain potential limitations. First and foremost, a meta-analysis inherits the limitations of the individual studies it is composed of. The quality of most of the papers examined appears to be no better or worse than other dietary studies. The mean quality score of the studies ($n = 48$) reported here was 33.7%, which is similar to the mean score (38.5%) from the assessment procedure outlined in the methods (58) and is similar to the mean score (35.5%) in a meta-analysis of glucosamine and chondroitin related to joint pain (46).

A second potential positive bias could be the nonreporting of negative studies. This is a very difficult issue to quantify. In the case of creatine and HMB, the shear numbers of papers published greatly diminish this potential. In contrast, where there is a small database such as DHEA and androstenedione, unpublished negative studies could have a major impact; but because the published studies on these supplements are largely neutral, the lack of publication of additional negative data would not likely change the overall conclusions.

Finally, another important limitation of this meta-analysis is the ability to generalize the effects of training status, age, and sex. The lack of repetition of each of these variables across all supplements precludes any definitive conclusion.

In summary, of the >250 dietary products available, only HMB and creatine supplements have sufficient scientific evidence to conclude that lean body mass and strength gains accompanying resistance training are augmented.

The authors thank Rowan Minnion for contribution in acquisition and analysis of data and assisting in preparation of the manuscript, Shawn Baier for contribution in preparation of the manuscript, Dr. Naji Abumrad for critical review of the manuscript, and Dr. Jerry Thomas for assistance in the statistical analysis of the data.

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APRIL 2003/Volume 94, Number 4

EDITORIAL

INVITED REVIEW

(Continued)

Cover: The April through June 2003 *Highlighted Topics* series explores genetic models. One such genetic model is the *Drosophila melanogaster*, which has been used for about 100 years. Based on high homology between the *Drosophila* and human genomes, substantial information can be obtained from such models to understand human biology and disease. We acknowledge Steve Graepel, illustrator of the cover design. This illustration is copyrighted by the Mayo Foundation and reproduced with permission.

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CORRIGENDA

Volume 94, February 2003

Pages 651–659: Steven L. Nissen and Rick L. Sharp. "Effect of dietary supplements on lean mass and strength gains with resistance exercise: a meta-analysis." The *Journal of Applied Physiology* has regretfully omitted a conflict of interest disclosure, which was provided by the author at the time of submission. The conflict of interest disclosure states as follows: Dr. Steven Nissen is a professor at Iowa State University, which owns the patents related to HMB. In addition, Dr. Nissen is the CEO of Metabolic Technologies, Inc., which is the licensee of the HMB patents. HMB is the subject of part of the meta-analysis.