



Substantial Skeletal Muscle Loss Occurs After Surgery⁽¹⁴⁾

The most muscle atrophy is seen during the initial 2 weeks post-op⁽³⁾

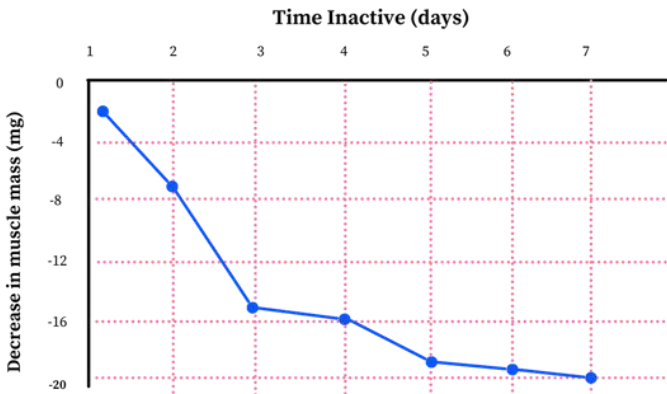
Decreased mobilization leads to further muscle atrophy:
0.5% /day in young
1.0% /day in elderly⁽¹⁸⁻²¹⁾

This catabolic state requires elevated (~80%) demands for essential amino acids [EAA].⁽²²⁾

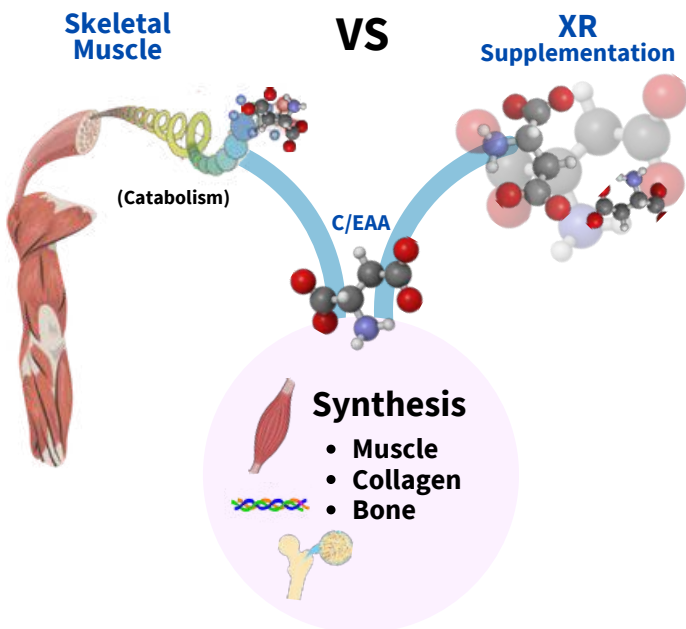
EAs serve as the necessary building blocks for collagen, bone and Muscle Protein Synthesis (MPS).⁽²³⁾

Without adequate nutritional support, the body harvests its only reserve (skeletal muscle) to provide these critical substrates for tissue healing.^(22-24,40)

XR™ is a targeted amino acid supplement formulated with clinically studied ingredients at optimal effective doses in preserving skeletal muscle during the catabolic state of surgery.



Kortebein, J Gerontol A Biol Sci Med Sci. 2008

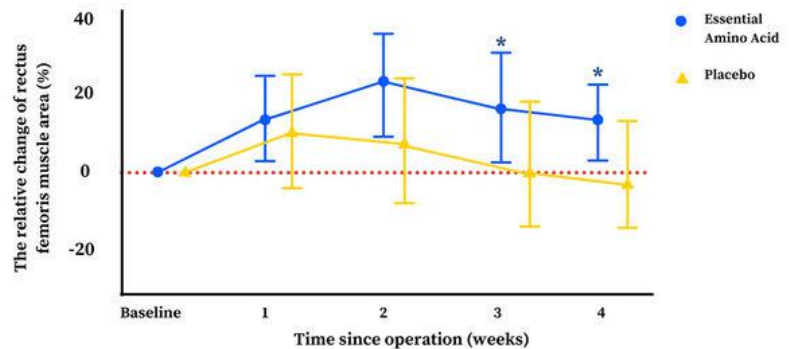


XR Basic Science/ Clinical Studies

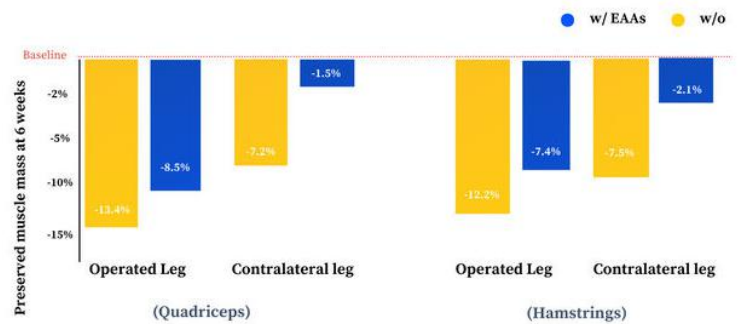
Essential Amino Acids (EAA)
EAA: ↑Muscle Protein Synthesis (MPS) via mTOR pathway ^(1,2)
EAA: ↑ # satellite (stem) muscle cell , ↓TNF- α (anti-inflammatory) ^(3,4,25)
Leucine: anabolic stimuli MPS via mTOR pathway ^(26,27)

Conditionally Essential Amino Acids (CEAA)
Glutamine: Anti-catabolic ↓ proteolysis, ↑collagen synthesis ⁽²³⁾
(HMB) β -Hydroxy β -methylbutyric: ⁽²⁸⁾ Anti-Catabolic, ↓ proteolysis
Arginine / Citrulline : ⁽²⁹⁻³⁴⁾ ↑endothelial NO production/↑collagen synthesis, ↑IGF-1, /↑ osteoblast activity / ↑ Fracture healing
Cystine /Theanine: Antioxidant, anti-catabolic ⁽³⁵⁻³⁹⁾

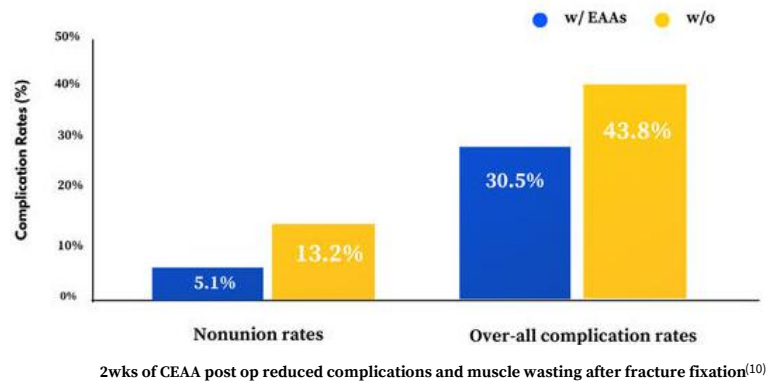
Clinical Applications	Results
TKA (*2020 Ranawat Award) ^(1,2) (1 wk pre- 2wks post-op)	↑Quad Volume ↑Strength ↑Albumin ↓Pain
TKA (1wk pre-2/6wks post-op) ^(3,4)	Preserve Muscle ↑Functional Recovery
Hip Fracture ^(5,6,44,45)	↑Albumin ↑Hemoglobin ↓Infection ↑Strength ↑Functional Recovery
ACL ⁽⁷⁾	↑Quad Volume ↑Strength
Trauma (Fracture fixation) ⁽¹⁰⁾ 2 wks post	Improved fracture union rates Decreased complications Preserved Muscle
TKA(5 days pre-28d post) ^(8,9)	↑Quad Volume ↑Strength
Collagen Deposition ^(12,13)	67% ↑Collagen Synthesis
Surgical Stress Suppression ⁽¹¹⁾ 5-10 days periop	↓CRP ↓IL-6
Diabetic foot ulcer ⁽¹⁵⁾	Shortened healing period ↓Use of antibiotics
(NASA) Countermeasure to Microgravity ⁽¹⁸⁾	Preserve Muscle Mass Mitigation of strength loss
Sarcopenia/ muscle wasting ^(16,17)	↑Lean body mass ↑Ablumin ↓Cortisol
Spine ⁽⁴¹⁻⁴³⁾	↑Strength ↑Wound healing ↓Infection ↑Fusion ↑IGF-1 ↑ Albumin



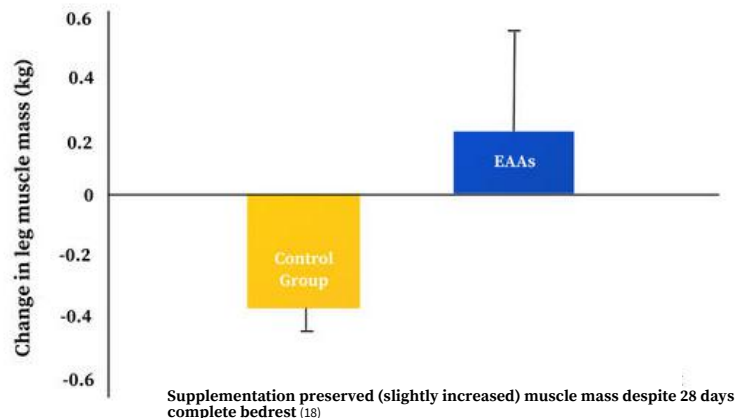
Patients who received EAAs 1 wk pre-op and 2 wks post-op had less muscle atrophy and early functional recovery after TKA ⁽²⁾



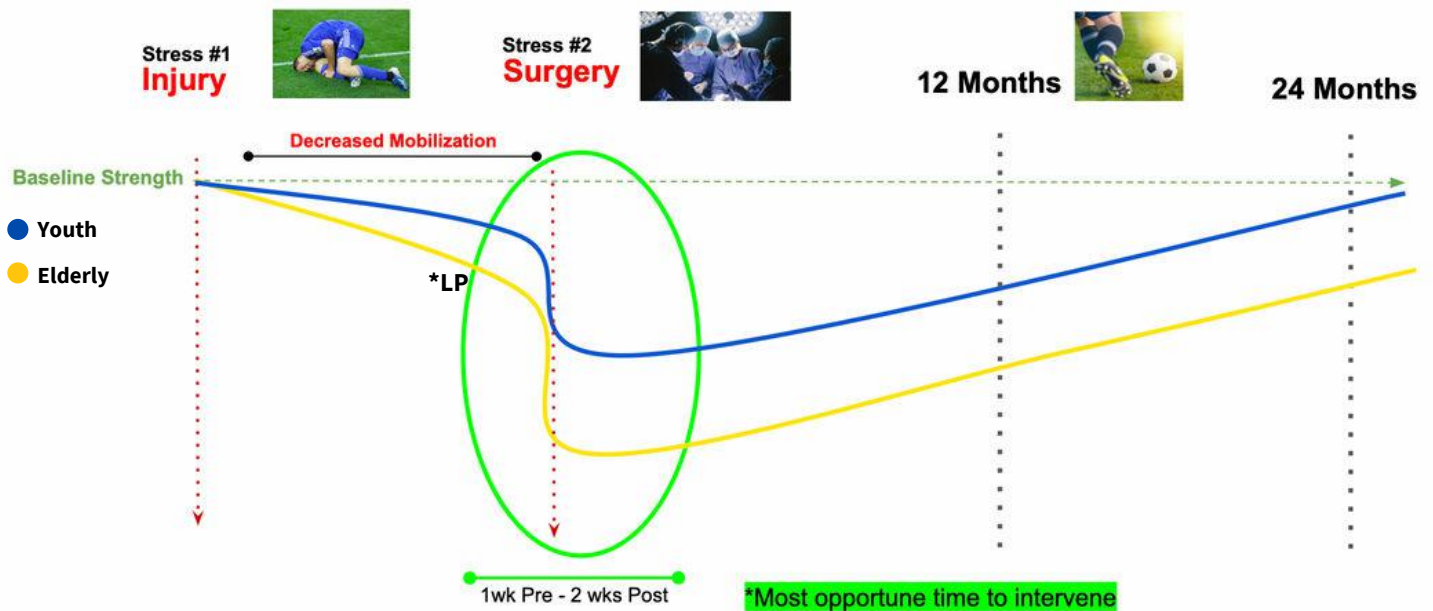
EAA group had significantly less decrease in mean muscle volume compared with the placebo group ⁽³⁾



2wks of CEAA post op reduced complications and muscle wasting after fracture fixation⁽¹⁰⁾



Supplementation preserved (slightly increased) muscle mass despite 28 days complete bedrest ⁽¹⁸⁾



*Loading Phase (1 week Pre-op)

Consumption of EAA for 1 week prior to surgery increases satellite (muscle stem) cells.⁽²⁵⁾

Preservation of muscle mass in the early post op period is predictive of muscle volume and strength at two years post-op.⁽²⁾

Skeletal muscle mass is both protective and predictive of post op complications and rate of functional recovery.^(1-4,6,8-10)



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MUSCULOSKELETAL
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Utilizing targeted amino acid supplementation provides essential substrates for tissue repair during recovery with evidence-backed benefits in mitigating muscle loss, reducing complications, and improving overall outcomes.

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References

- (1) Ueyama H, Kanemoto N, Minoda Y, Taniguchi Y, Nakamura H. 2020 Chitranjan S. Ranawat Award: Perioperative essential amino acid supplementation suppresses rectus femoris muscle atrophy and accelerates early functional recovery following total knee arthroplasty. *Bone Joint J.* 2020 Jun
- (2) Ueyama H, Kanemoto N, Minoda Y, Taniguchi Y, Nakamura H. Perioperative Essential Amino Acid Supplementation Facilitates Quadriceps Muscle Strength and Volume Recovery After TKA: A Double-Blinded Randomized Controlled Trial. *J Bone Joint Surg Am.* 2023 Mar 1;105(5):345-353. doi: 10.2106/JBJS.22.00675. Epub 2023 Mar 1. PMID: 36856692.
- (3) Dreyer HC, Owen EC, Strycker LA, Smolkowski K, Muyskens JB, Kirkpatrick TK, Christie AD, Kuehl KS, Lantz BA, Shah SN, Mohler CG, Jewett BA. Essential Amino Acid Supplementation Mitigates Muscle Atrophy After Total Knee Arthroplasty: A Randomized, Double-Blind, Placebo-Controlled Trial. *JB JS Open Access.* 2018 Jun 4;3(2):e0006. doi: 10.2106/JBJS.OA.18.00006. PMID: 30280129; PMCID: PMC6145559.
- (4) Dreyer HC, Strycker LA, Senesac HA, Hocker AD, Smolkowski K, Shah SN, Jewett BA. Essential amino acid supplementation in patients following total knee arthroplasty. *J Clin Invest.* 2013 Nov;123(11):4654-66. doi: 10.1172/JCI70160. Epub 2013 Oct 25. PMID: 24135139; PMCID: PMC3809795.
- (5) Roberto Aquilani 1, Ginetto Carlo Zuccarelli 2, Anna Maria Condino 3, Michele Catani 2, Carla Rutili 2, Consiglia Del Vecchio 2, Pietro Pisano 2, Manuela Verri 1, Paolo Iadarola 4, Simona Viglio 5 and Federica Boschi 3,*Despite Inflammation, Supplemented Essential Amino Acids May Improve Circulating Levels of Albumin and Hemoglobin in Patients after Hip Fractures *Nutrients* 2017, 9, 637
- (6) Roberto Aquilani, Carlo Zuccarelli Ginetto, Carla Rutili, Pietro Pisano, Evasio Pasini, Eleonora Baldissarro, Manuela Verri, Federica Boschi Supplemented amino acids may enhance the walking recovery of elderly subjects after hip fracture surgery *Aging Clinical and Experimental Research* Received: 17 November 2017 / Accepted: 27 March 2018
- (7) Laboute E, France J, Trouve P, Puig PL, Boireau M, Blanchard A. Rehabilitation and leucine supplementation as possible contributors to an athlete's muscle strength in the reathletization phase following anterior cruciate ligament surgery. *Ann Phys Rehabil Med.* 2013 Mar;56(2):102-12. doi: 10.1016/j.rehab.2012.11.002. Epub 2012 Dec 6. PMID: 23260415.
- (8) Malafarina V, Uriz-Otano F, Malafarina C, Martinez JA, Zulet MA. Effectiveness of nutritional supplementation on sarcopenia and recovery in hip fracture patients. A multi-centre randomized trial. *Maturitas.* 2017 Jul;101:42-50. doi: 10.1016/j.maturitas.2017.04.010. Epub 2017 Apr 22. PMID: 28539168.
- (9) Kanae Nishizaki PT., Hitoshi Ikegami MD, Yukio Tanaka MD, Ryutaro Imai MD, Hajime Matsumura MD, DMSc, FACS Effects of supplementation with a combination of β -hydroxy- β -methyl butyrate, L-arginine, and L-glutamine on postoperative recovery of quadriceps muscle strength after total knee arthroplasty *Asia Pac J Clin Nutr* 2015;24(3):412-420
- (10) Hendrickson NR, Davison J, Glass NA, Wilson ES, Miller A, Leary S, Lorentzen W, Karam MD, Hogue M, Marsh JL, Willey MC. Conditionally Essential Amino Acid Supplementation Reduces Postoperative Complications and Muscle Wasting After Fracture Fixation: A Randomized Controlled Trial. *J Bone Joint Surg Am.* 2022 May
- (11) Williams JZ, Barbul A. Nutrition and wound healing. *Surg Clin North Am.* 2003;83:571-596
- (12) Okamoto H, Taniyama Y, Sakurai T, Kodama G, Sato C, Fukutomi T, Ozawa Y, Ishida H, Koseki K, Yamauchi T, Nakano T, Unno M, Kamei T. Perioperative Administration of Cystine and Theanine Suppresses Inflammation and Facilitates Early Rehabilitation and Recovery after Esophagectomy: A Randomized, Double-Blind, Controlled Clinical Trial. *Nutrients.* 2022 May 31;14(11):2319. doi: 10.3390/nu14112319. PMID: 35684118; PMCID: PMC9182838.
- (13) Tsuchiya T, Kurihara S. Cystine and Theanine as Stress-Reducing Amino Acids-Perioperative Use for Early Recovery after Surgical Stress. *Nutrients.* 2021 Dec 28;14(1):129. doi: 10.3390/nu14010129. PMID: 35011010; PMCID: PMC8746811.
- (14) Willey, Michael C. MD1,a; Owen, Erin C. PhD, MPH2; Miller, Aspen BS1; Glass, Natalie PhD1; Kirkpatrick, Tessa BS2; Fitzpatrick, Daniel MD2; Wilken, Jason PhD1; Marsh, J. Lawrence MD1; Reider, Lisa PhD3. Substantial Loss of Skeletal Muscle Mass Occurs After Femoral Fragility Fracture. *The Journal of Bone and Joint Surgery* 105(22):p 1777-1785, November 15, 2023. | DOI: 10.2106/JBJS.23.00353
- (15) Tatti, P., & Barber, A. (2012). The Use of a Specialized Nutritional Supplement for Diabetic Foot Ulcers Reduces the Use of Antibiotics. *Journal Of Endocrinology And Metabolism*, 2(1), 26-31.
- (16) Hsieh LC, Chow CJ, Chang WC, Liu TH, Chang CK. Effect of beta-hydroxy-beta-methylbutyrate on protein metabolism in bed-ridden elderly receiving tube feeding. *Asia Pac J Clin Nutr.* 2010;19(2):200-8. PMID: 20460233.
- (17) Rathmacher JA, Nissen S, Pantoni L, Clark RH, Eubanks May P, Barber AE, D'Olimpio J, Abumrad NN. Supplementation with a combination of beta-hydroxy-beta-methylbutyrate (HMB), arginine, and glutamine is safe and could improve hematological parameters. *JPEN J Parenter Enteral Nutr.* 2004 Mar-Apr;28(2):65-75. doi: 10.1177/014860710402800265. PMID: 15080599.
- (18) Paddon-Jones D, Sheffield-Moore M, Urban RJ, et al: Essential amino acid and carbohydrate supplementation ameliorates muscle protein loss in humans during 28 days bedrest. *J Clin Endocrinol Metab* 2004;89:4351-4358
- (19) Kortebein P, Symons TB, Ferrando A, et al., *J Gerontol A Biol Sci Med Sci.* 2008;63(10):1076-1081.
- (20) Kortebein P, Ferrando A, Lombardi J, et al: Effect of 10 days of bed rest on skeletal muscle in healthy older adults. *JAMA* 2007;297:1772-1774.
- (21) Paddon-Jones D, Sheffield-Moore M, Cree MG, et al: Atrophy and impaired muscle protein synthesis during prolonged inactivity and stress. *J Clin Endocrinol Metab* 2006;91:4836-4841
- (22) Smith-Ryan AE, Hirsch KR, Saylor HE, Gould LM, Blue MNM. Nutritional Considerations and Strategies to Facilitate Injury Recovery and Rehabilitation. *J Athl Train.* 2020 Sep 1;55(9):918-930. doi: 10.4085/1062-6050-550-19. PMID: 32991705; PMCID: PMC7534941.
- (23) Arribas-López E, Zand N, Ojo O, Snowden MJ, Kochhar T. The Effect of Amino Acids on Wound Healing: A Systematic Review and Meta-Analysis on Arginine and Glutamine. *Nutrients.* 2021 Jul 22;13(8):2498. doi: 10.3390/nu13082498. PMID: 34444657; PMCID: PMC8399682.
- (24) Hirsch KR, Wolfe RR, Ferrando AA. Pre- and Post-Surgical Nutrition for Preservation of Muscle Mass, Strength, and Functionality Following Orthopedic Surgery. *Nutrients.* 2021 May 15;13(5):1675. doi: 10.3390/nu13051675. PMID: 34063333; PMCID: PMC8156786.
- (25) Muyskens JB, Foote DM, Bigot NJ, Strycker LA, Smolkowski K, Kirkpatrick TK, Lantz BA, Shah SN, Mohler CG, Jewett BA, Owen EC, Dreyer HC. Cellular and morphological changes with EAA supplementation before and after total knee arthroplasty. *J Appl Physiol* (1985). 2019 Aug 1;127(2):531-545. doi: 10.1152/jappphysiol.00869.2018. Epub 2019 Jul 25. PMID: 31343947; PMCID: PMC6732445.

References

- (26) Drummond MJ, Rasmussen BB. Leucine-enriched nutrients and the regulation of mammalian target of rapamycin signalling and human skeletal muscle protein synthesis. *Curr Opin Clin Nutr Metab Care*. 2008 May;11(3):222-6. doi: 10.1097/MCO.0b013e3282fa17fb. PMID: 18403916; PMCID: PMC5096790.
- (27) Kimball SR, Jefferson LS. Signaling pathways and molecular mechanisms through which branched-chain amino acids mediate translational control of protein synthesis. *J Nutr*. 2006 Jan;136(1 Suppl):227S-31S. doi: 10.1093/jn/136.1.227S. PMID: 16365087.
- (28) Bear DE, Rooyackers O. HMB and leucine supplementation during critical illness and recovery. *Curr Opin Clin Nutr Metab Care*. 2022 Mar 1;25(2):88-92. doi: 10.1097/MCO.0000000000000809. PMID: 34937852.
- (29) Ardiansyah A, Dilogo IH, Gunawan B, Oesman I, Herlambang D. Functional, radiological, and quality of life outcome of unstable acetabular fracture with quadrilateral plate involvement at a tertiary care center in Jakarta, Indonesia. *Eur J Orthop Surg Traumatol*. 2023 Nov 15. doi: 10.1007/s00590-023-03752-2. Epub ahead of print. PMID: 37966556.
- (30) Meesters DM, Wijnands KAP, Brink PRG, Poeze M. Malnutrition and Fracture Healing: Are Specific Deficiencies in Amino Acids Important in Nonunion Development? *Nutrients*. 2018 Oct 31;10(11):1597. doi: 10.3390/nu10111597. PMID: 30384490; PMCID: PMC6266771.
- (31) Kdolsky RK, Mohr W, Savidis-Dacho H, Beer R, Puig S, Reihnsner R, Tangl S, Donath K. The influence of oral L-arginine on fracture healing: an animal study. *Wien Klin Wochenschr*. 2005 Oct;117(19-20):693-701. doi: 10.1007/s00508-005-0431-y. PMID: 16416369.
- (32) Torricelli P, Fini M, Giavaresi G, Giardino R. Bone tissue cultures: an in vitro model for the evaluation of bone defect healing after L-arginine and L-lysine administration. *Artif Cells Blood Substit Immobil Biotechnol*. 2001 Jul;29(4):325-34. doi: 10.1081/bio-100104234. PMID: 11495013.
- (33) Hughes MS, Kazmier P, Burd TA, Anglen J, Stoker AM, Kuroki K, Carson WL, Cook JL. Enhanced fracture and soft-tissue healing by means of anabolic dietary supplementation. *J Bone Joint Surg Am*. 2006 Nov;88(11):2386-94. doi: 10.2106/JBJS.F.00507. PMID: 17079395.
- (34) Yaman F, Acikan I, Dundar S, Simsek S, Gul M, Ozercan IH, Komorowski J, Sahin K. Dietary arginine silicate inositol complex increased bone healing: histologic and histomorphometric study. *Drug Des Devel Ther*. 2016 Jun 27;10:2081-6. doi: 10.2147/DDDT.S109271. PMID: 27390517; PMCID: PMC4930222.
- (35) Miyachi T, Tsuchiya T, Oyama A, Tsuchiya T, Abe N, Sato A, Chiba Y, Kurihara S, Shibakusa T, Mikami T. Perioperative oral administration of cystine and theanine enhances recovery after distal gastrectomy: a prospective randomized trial. *JPEN J Parenter Enteral Nutr*. 2013 May-Jun;37(3):384-91. doi: 10.1177/0148607112458798. Epub 2012 Sep 12. PMID: 22972879.
- (36) Murakami S, Kurihara S, Titchenal CA, Ohtani M. Suppression of exercise-induced neutrophilia and lymphopenia in athletes by cystine/theanine intake: a randomized, double-blind, placebo-controlled trial. *J Int Soc Sports Nutr*. 2010 Jun 4;7(1):23. doi: 10.1186/1550-2783-7-23. PMID: 20525371; PMCID: PMC2892463.
- (37) Kawada, S, Kobayashi, K, Ohtani, M, Fukusaki, C. Cystine and theanine supplementation restores high-intensity resistance exercise-induced attenuation of natural killer cell activity in well-trained men. *J Strength Cond Res* 2010;24:846-85
- (38) Murakami S, Kurihara S, Koikawa N, Nakamura A, Aoki K, Yosigi H, Sawaki K, Ohtani M. Effects of oral supplementation with cystine and theanine on the immune function of athletes in endurance exercise: randomized, double-blind, placebo-controlled trial. *Biosci Biotechnol Biochem*. 2009 Apr 23;73(4):817-21. doi: 10.1271/bbb.80663. Epub 2009 Apr 7. PMID: 19352043.
- (39) Tsuchiya, T, Kurihara, S: Cystine and Theanine as Stress-Reducing Amino Acids-Perioperative Use for Early Recovery after Surgical Stress. *Nutrients* 2021;14:129.
- (40) Demling RH. Nutrition, anabolism, and the wound healing process: an overview. *Eplasty*. 2009;9:e9. Epub 2009 Feb 3. PMID: 19274069; PMCID: PMC2642618.
- (41) Minetama M, Kawakami M, Teraguchi M, Enyo Y, Nakagawa M, Yamamoto Y, Sakon N, Matsuo S, Nakatani T, Nakagawa R, Nagata W, Nakagawa Y. Branched-chain amino acids plus vitamin D supplementation promote increased muscle strength following lumbar surgery for lumbar spinal stenosis: a randomized trial. *Spine J*. 2023 Jul;23(7):962-972. doi: 10.1016/j.spinee.2023.03.007. Epub 2023 Mar 20. PMID: 36940921.
- (42) Khalooeifard R, Oraee-Yazdani S, Keikhaee M, Shariatpanahi ZV. Protein Supplement and Enhanced Recovery After Posterior Spine Fusion Surgery: A Randomized, Double-blind, Placebo-controlled Trial. *Clin Spine Surg*. 2022 Apr 1;35(3):E356-E362. doi: 10.1097/BSD.0000000000001222. PMID: 34379607.
- (43) Khalooeifard R, Shariatpanahi ZV, Ahani A, Keykhaee M, Oraee-Yazdani M, Zali A, Oraee-Yazdani S. Effect of Protein Supplement on Paraspinal Muscles in Spine Fusion Surgery: A Randomized, Double-Blind, Placebo-Controlled Trial. *Int J Spine Surg*. 2021 Feb;15(1):47-54. doi: 10.14444/8005. Epub 2021 Feb 18. PMID: 33900956; PMCID: PMC7931746.
- (44) Invernizzi M, de Sire A, D'Andrea F, Carrera D, Renò F, Migliaccio S, Iolascon G, Cisari C. Effects of essential amino acid supplementation and rehabilitation on functioning in hip fracture patients: a pilot randomized controlled trial. *Aging Clin Exp Res*. 2019 Oct;31(10):1517-1524. doi: 10.1007/s40520-018-1090-y. Epub 2018 Dec 11. PMID: 30539540.
- (45) Liu M, Yang J, Yu X, Huang X, Vaidya S, Huang F, Xiang Z. The role of perioperative oral nutritional supplementation in elderly patients after hip surgery. *Clin Interv Aging*. 2015 May 11;10:849-58. doi: 10.2147/CIA.S74951. PMID: 26005339; PMCID: PMC4433048.