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Review Article

Essential amino acids in total knee and hip joint replacement: a narrative review

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ABSTRACT

The increasing availability of total joint replacement especially for knee and hip joints has increased their rates substantially across the globe. It is associated with increased risk of sarcopenia with loss of muscle mass and strength in the postoperative period. The supplementation of proteins along with exercises have been mainframe strategy to improve the functional ability after total knee arthroplasty and total hip arthroplasty. However, supplementation of proteins necessitates effective proteolytic digestion and conversion to amino acids for exerting substantial effects. In overcoming this challenge, supplementation with essential amino acids can be an attractive approach In this article, we review the clinical evidence with use of essential amino acids in patients undergoing TKA and THA. In the nine studies included in the review, seven assessed EAAs in TKA and two in THA. In TKA studies, improvement in muscle mass, muscle strength and functional recovery has been significant over 6 weeks postoperatively in majority of the studies. Over long term (2 years), improved recovery of rectus femoris and quadriceps had been reported. In THA as well, significant improvement in hip function and stability has been reported. Thus, EAAs in addition to the existing rehabilitation program are helpful to improve sarcopenia and enhances the recovery to perform activities of daily living. We propose from current evidence that administration of EAAs 7 to 10 days prior to planned TKA or THA and continued for 14 to 20 days in the postoperative period along with rehabilitation program is optimal in enhancing the muscle strength and help in physical functional recovery. Current evidence indicates supplementation with EAAs should be a part of routine management protocol in patients undergoing TKA or THA.

Keywords: Essential amino acids, Total knee arthroplasty, Total hip arthroplasty, Joint replacement, Nutrition

INTRODUCTION

Joint replacement therapy has evolved substantially over last two decades with total hip arthroplasty (THA) and total knee arthroplasty (TKA) being performed widely across the globe.[1,2] In India, the rate of TKAs increased from 1019 in 2006 to 27,000 in the year 2019.[3] Irrespective of the major indications such as osteoarthritis (OA), and rheumatoid arthritis, surgical joint replacement such as TKA and THA have shown to be effective in terms of pain, mobility and stability among patients who do not respond to conservative and medical management.[4-7] Nonetheless, these procedures carry risk of various complications such as dislocations, infections and thromboembolic events.[8,9] Patients who undergo such joint replacement procedures have significant effect on muscle function of the lower limbs.[10-12] Thus, intensive rehabilitation and physical therapy such as aquatic therapy, ergometer cycling, and fast-track protocols are advocated to all patients with TKA and THA.[13] Optimization of nutritional status in the

preoperative period can assist in managing the surgical stress response and muscle function especially in undernourished, or elderly people.[14] Supplementation of essential amino acids (EAAs) in patients who have undergone knee surgeries such as TKA or anterior cruciate ligament repair increases the strength and muscle mass.[15] In this review, we review mechanisms of sarcopenia, role of EAAs in sarcopenia and briefly review the current clinical evidence assessing the impact of EAAs supplementation on muscle strength and function in patients undergoing TKA and THA.

SARCOPENIA AND ROLE OF ESSENTIAL AMINO ACIDS

In general, sarcopenia occurs with ageing that is associated with progressive loss in both muscle mass and strength. Knee osteoarthritis, prevalent in the elderly, doubles the risk of sarcopenia compared to those without OA.[16] In OA, articular cartilage, synovium, and ligaments all show changes of degeneration indicating similar pathology involving these structures in OA. In such patients, muscle loss is frequent with atrophy of muscle fibre. In turn, muscle loss leads to joint instability and further affects the articular cartilage degeneration.[17] OA patients undergoing TKA or THA surgeries have an increased risk of loss in muscle mass in the postoperative period.[11,18] The pathophysiological mechanisms involve genetic and metabolic alterations. Muscle loss incites metabolic insult resulting in altered gene expression, impaired turnover of muscle proteins, dysregulated autophagy, increased anabolic resistance and reduced satellite cell regeneration. These alterations contribute to muscle atrophy with reduced muscle activation.[19-22] In managing the muscle loss after TKA or THA, there are no specific therapies and thus, early rehabilitation with exercise and nutritional intervention have been suggested. Combined, resistance exercises and protein supplementation, have shown benefits in muscle mass and strength recovery in postoperative period.[23-25] However, supplementation of proteins necessitates effective proteolytic digestion and conversion to amino acids for exerting substantial effects. In overcoming this challenge, supplementation with essential amino acids (EAAs) can be an attractive approach. Supplementation of EAAs results in increased muscle mass, muscle strength, reduced protein degradation, improved anabolic metabolism in muscles, increased myogenic genes expression, and stimulation of myosin heavy chain and myogenic expression along with increased satellite cell content and regeneration contributing to improved overall muscle functioning.[26-29] The (Figure 1) schematically represents the possible actions exerted by EAAs in muscle functioning.

CLINICAL EVIDENCE REVIEW METHODOLOGY

Search strategy and results

We searched bio-medical databases such as PubMed, Cochrane Central Register of Controlled trials, and Google Scholar with key terms such as Essential Amino Acids, Total Knee Arthroplasty, Total Hip Arthroplasty, Hip Joint Replacement, Knee Joint Replacement, Muscle Function, Muscle Mass, Muscle Strength and used these keywords in combination using various Boolean operators. With detailed search of listed databases, we identified nine studies for inclusion in this review.[30-38] Among the included studies, seven evaluated EAAs in TKA.[30-36] and two assessed in THA.[37,38] Findings from these studies are briefed and reviewed in below sections.

Clinical evidence: studies in TKA

In a placebo-controlled randomized study, Hocker and colleagues assessed effect of preoperative EAAs supplementation on expression of amino acid (AA) transporter gene and total protein levels in patients undergoing TKA.[30] Participants were preoperatively administered either 20 gm EAAs (N=9) or placebo (N=7). With an overnight fast, each participants muscle biopsies were performed just before TKA. Using quantitative PCR and Western blot techniques, authors observed significantly higher expression of transcript and protein expression for AA transporters. Compared to placebo, EAA group had significantly higher mRNA levels for SNAT2, SNAT4, LAT3. These results indicate that EAAs may increase the AA transporters in patients undergoing TKA. A study from Muyskens et al assessed the cellular mechanisms behind muscle atrophy in patients with TKA. A total of 41 patients, aged 53 to 76 years, scheduled for TKA received either EAAs (20 g) or placebo twice daily for 7 days prior to the procedure and for 6 weeks thereafter.[31]

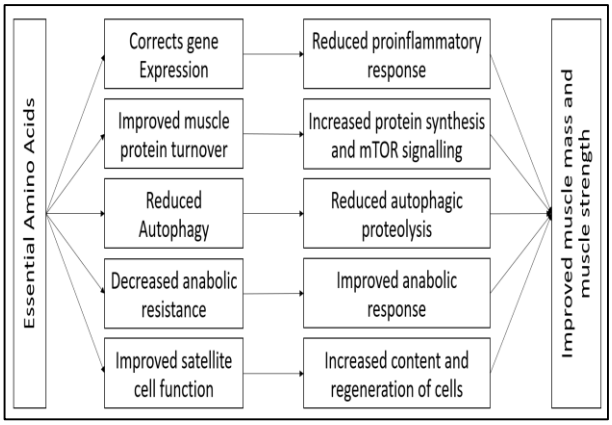

Figure 1: Effects of essential amino acids in muscles.

The evaluation was based on satellite cells and other important histology indicators of inflammation, fibrosis, and recovery. Prior to surgery in the operating room, a first set of muscle samples was taken from both legs. Patients were then randomly assigned to groups and proportionally allocated to have two more biopsies at either 1 or 2 week after surgery. Immunohistochemistry and gene expression analysis were performed on biopsies. Patients of the EAA group had significantly higher levels of satellite cells than

placebo group. The histological evaluation did not reveal any significant difference in the fibrotic tissues, either pre-surgery or post-surgery. Gene expression of myogenic regulatory factors varied between the groups, with increased MyoD expression in placebo and increased Myogenin expression in EAA group at 1-week post-surgery. Placebo group had a higher concentration of M1 macrophages than the EAA group. Transcript levels of IL-6 and TNF were increased in both groups postoperatively, while TNF decreased in the EAA group after 2 weeks. Beginning 7 days prior to surgery, EAAs enhanced satellite cells on the day of surgery and encouraged a more hospitable inflammatory state after surgery. Study stressed that in elderly undergoing TKA, the bulk of muscle atrophy happens quickly, during the first two weeks and EAAs supplementation before surgery has a beneficial impact on inflammation indicators.

In further understanding of the genetic linkage of muscle atrophy following TKA and effect of EAAs, Muyskens et al performed RNA-sequencing (RNA-seq) to find the genes linked to atrophy following TKA with and without EAAs.[32] A total of 156 samples were obtained (41 subjects x 4 biopsies per subject) and analysed for genetic assessments. Study results revealed that after TKA, the p53 signalling and cytokine-cytokine receptor mechanisms were significantly elevated. Some of the genes involved in muscle loss were BBC3, BCL2A1, BIRC3, BIRC5, CASP10, CCN1, CDC14A, PMAIP1, CCL3, CCR1, CCR5, CX3CL1, CXCL1, CXCL16, TNFRSF10A, TRIM22, ATM, ATR, AURKB, BAZ1A, BRCA2, CEBPA, PTEN, SIRT7, CCNB2, CCND1, MYC, FDXR, FUCA1, and PPARGC1A. Compared with the placebo group, the EAAs supplementation changed expression of MDM2 and other p53 regulators. Authors stated that due to changes in the timing of overexpression of some p53 targets, such as apoptotic genes, between groups, this changed expression may be to blame for individuals receiving EAAs seeing less muscle loss. The expression of many cytokine-signalling genes, including TNFRSF12A, which is essential for the wasting of muscles, fibrosis, myogenesis, and the noncanonical NF-kB pathway was also found to be altered. These results indicate that EAAs possibly can influence the cytokine and p53-dependent gene expression following surgery and thereby halting or reducing the atrophy of limb muscles.

In a prospective, double-blind, randomized trial, Dryer and colleagues enrolled patients aged 53-76 years undergoing primary unilateral TKA.[33] A total of 39 patients received in a 1:1 ratio 20 g of EAAs (N=19) or a placebo (N=20) twice a day. EAAs supplementation or placebo was begun one week before TKA, stopped on the day of surgery, restarted on the first postoperative day, and continued for a total of 6 weeks. Preoperative blood chemistry, MRI, strength and functional mobility, and patient-reported outcomes; Knee Injury and Osteoarthritis Outcome Score (KOOS) and Veterans RAND 12-Item Health Survey (VR-12) data were all collected at baseline (2–6 weeks prior to surgery) and were also followed up during the healing process.[33] Blinded MRI data was collected, and mid-thigh muscle volume was determined. In the analysis, 64% were females and 95% were non-Hispanic white (64.41±0.94 years, baseline BMI of 29.78±1.20 kg/m^2, tourniquet time of 56.18±3.74 minutes, and operational time of 94.74±3.18 minutes). Regardless of the treatment, there were significant changes in mean muscle volume for the quadriceps and hamstrings muscles from baseline to 6 weeks postoperatively ($p<0.05$). In comparison to the EAA group, quadriceps muscular atrophy was considerably higher in the placebo group in both legs (213.4±1.9% vs. 28.5±2.5%; $p=0.033$) and the contralateral leg (27.2±1.4% vs. 21.5±1.6%; $p=0.014$). Furthermore, hamstring muscle atrophy was substantially higher in the placebo than EAA group in both legs (212.2±1.4% vs. 27.4±2.0%; $p=0.036$) and the contralateral leg (27.5±1.5% vs. 22.1±1.3%; $p=0.005$). Functional assessments and patient-reported outcome measures (PROMs) did not change substantially from baseline to 6 weeks postoperatively for either group. The strength, functional mobility, and PROMs in the quadriceps and hamstrings showed no discernible postoperative therapy effects. The average daily energy expenditure in the placebo and EAA groups was the same before surgery (319.71±56.97 vs. 408.15±45.37 kcal/day; $p=0.24$) and after surgery. Dietary calorie consumption considerably decreased in both groups from baseline to 2 weeks after surgery ($p<0.05$), but not until 6 weeks after surgery ($p>0.05$). In addition, there were neither adverse study-related events nor discernible differences between the groups in non-study-related adverse events. Overall, the study favoured safe EAA supplementation and prevention of muscle volume loss in elderly people recovering from TKA.

In a similar randomized controlled trial, Nishizaki et al examined the effects of supplementation with a combination of L-arginine, β-hydroxy-β-methyl butyrate (HMB), and glutamine (HMB/Arg/Gln) on the recovery of quadriceps muscular strength following TKA.[34] A total of 23 patients with knee osteoarthritis who were 65 to 80 years old were enrolled. The experiment group (N=13) received daily HMB/Arg/Gln supplementation for 5 days prior to surgery and 28 days following surgery, whereas the control group (N=10) received orange juice. Strength training and range-of-motion exercises were started as part of the rehabilitation process on the first postoperative day, and walking training from the second postoperative day continued for 5 days a week during hospitalization.

At various time intervals, total exercise, isometric contraction, and muscle strength tests measurements were computed. Additionally, body weight, computed tomography scan measurements, caloric consumption, and supplement intake quantities were noted. There were no discernible changes between the groups in terms of body weight, knee extension strength, muscle area, or overall energy expenditure. The recovery duration was 12.8±3.2 days for the control and 13.1±2.4 days for the HMB/Arg/Gln group, respectively ($p=0.54$).

Table 1: Clinical studies assessing utility of essential amino acids in TKA and THA.

Author	Design	Population	Intervention	Major findings
Dreyer et al.[33]	RCT	TKA	20 g of EAA (N=19) or placebo (N=20) BID preoperatively for 7 days and postoperatively 6 weeks	Significant change in mean muscle volume for the quadriceps and hamstrings in EAA group than placebo
Nishizaki et al.[34]	RCT	TKA	L-arginine, β-hydroxy-β-methyl butyrate (HMB), and glutamine (HMB/ Arg/Gln) (N=13) vs. orange juice (N=10), 5 days prior and 28 days following surgery	No significant loss in the cross-sectional area of the rectus femoris with EAA: -4.3±26.2% in the control group and + 10.0±20.5% in the HMB/Arg/Gln group
Ueyama et al.[35]	RCT	TKA	EAAs (9 g/day) and powdered lactose (9 g/day, placebo) for 7 days before and 14 days after surgery	Two years after surgery: Rectus femoris area was significant greater with EAAs (134±31% vs. 114±27%, $p<0.05$). Strengths of the quadriceps muscle was significantly higher with EAAs (159±54% vs. 125±40%, $p<0.05$)
Pandor et al.[36]	Observational study	TKA	EAA (N=10) or placebo (N=10), three capsules twice daily from 1 week before to 6 weeks after TKA	Quadriceps and hamstrings muscle volume assessed by MRI showed significant improvement in both groups. For involved leg, atrophy of the quadriceps (-11.2±1.9% vs. -8.5±2.5%; p=0.014) and hamstring (-10.2±1.4% vs.-7.4±2.0%; p= 0.026) was significantly higher in the placebo group than EAA group. Significant reduction in time for 6-metre walk distance in EAA group (8.9±1.7 sec at 2-week pre-operatively to 6.9±1.5 sec. at 6-weeks post-operatively, p=0.0121) but not in placebo group (8.7±1.24 sec. to 7.5±1.34 sec., p=0.0522)
Aquilani et al.[37]	RCT	THA	Rehabilitation only (Rehab, N=27); rehabilitation and placebo (RP, N=28) or rehabilitation and EAAs (RE, 8 g/day, N=28)	Significantly higher rate of achieving average improvement in walking distance exceeding the threshold of clinical significance by +50 meters with RE than RP or Rehab only (pairwise comparison: RE versus RP: p=0.024; RE vs Rehab: p=0.034; RP vs Rehab: p=0.9). Higher proportion of patients with EAA (75%) achieved +50 m distance than RP (46.4%) and Rehab (66.7%)
Baldissarro et al.[38]	RCT	THA	EAAs (8 gm/day) (N=30) or placebo (maltodextrin) (N=30) for 14 days, Healthy controls (N=10)	Significant functional recovery - significant change in HHS test in EAA group (41.8±1.15 at admission to 76.37±6.6 at discharge) than placebo (at admission 39.78±4.89 to 70±7.1 at discharge), (p=0.006)

There was no discernible difference in the length of hospital stays (19.1±3.7 and 18.9±3.3 days, respectively, p=0.85). The HMB/Arg/Gln group's 1-day mean total calorie consumption was 1,765±107 kcal, compared to 1,737±104 kcal for the control group. The HMB/Arg/Gln group's mean body weight fluctuated between 63.6±10.7 kg at the beginning and 62.7±10.2 kg at the conclusion. Although the difference was not statistically significant, there was a propensity to lose weight (p=0.06). Between the day before surgery and postoperative day 14, the control group showed a substantial decline in muscular strength (p=0.02). There was no significant difference between the preoperative and postoperative muscular strength measurements in the HMB/Arg/Gln group. The

cross-sectional area of the rectus femoris was -4.3±26.2% in the control group and 10.0±20.5% in the HMB/Arg/Gln group. The HMB/Arg/Gln group had an upward trend (p=0.15). There was no statistically significant difference between the decrease in the cross-sectional area of the unoperated side in the HMB/Arg/Gln group and the control group. Overall, supplements of HMB/Arg/Gln may prevent the loss of muscular strength following TKA though patients need maintenance of their quadriceps strength with intervention through exercise and diet.

In another double-blind, randomized controlled trial, Ueyama et al evaluated 60 TKA patients who received EAAs (9 g/day) and powdered lactose (9 g/day, placebo) for 7 days before and 14 days after surgery.[35] They evaluated the recovery of leg muscles. Study was designed with baseline measurements before surgery and periodical follow-up up to two years after surgery. Authors considered 100% as baseline value for the muscle area. At 2 years after surgery, the increment in the rectus femoris area measured using ultrasonography was statistically significant with EAAs (134±31% vs. 114±27%, p<0.05). Similarly, improvement of strengths of the quadriceps muscle measured by dynamometer was significantly higher with EAAs than placebo (159±54% vs. 125±40%, p<0.05). Clinical outcomes in terms of pain, range of motion, functional mobility, and KSS scores did not differ in two groups. Thus, in TKA patients, EAAs supplementation results in significant recovery of the rectus femoris and quadriceps muscles. In a study from Pandor et al 20 patients (aged 50 to 70 years) undergoing TKA received either EAA (N=10) or placebo (N=10), three capsules twice daily from 1 week before to 6 weeks after TKA.[36] EAA consisted of L-leucine (1020 mg), L-valine (510 mg), L-lysine (450 mg), L-isoleucine (510 mg), L-phenylalanine (300 mg), L-threonine (180 mg), and L-tryptophan (30 mg). Muscle volume assessed by the magnetic resonance imaging of the quadriceps and hamstrings showed significant improvement in both groups. However, the atrophy of the quadriceps (-11.2±1.9% vs. -8.5±2.5%; p=0.014) and hamstring (-10.2±1.4% vs.-7.4±2.0%; p=0.026) was significantly higher in the placebo group than EAA group for involved leg. Similarly, atrophy was significantly greater in contralateral leg as well. At 6 weeks, there was significant reduction in time for 6-metre walk distance in EAA group (8.9±1.7 sec at 2-week pre-operatively to 6.9±1.5 sec. at 6-weeks post-operatively, p=0.0121) but not in placebo group (8.7±1.24 sec. to 7.5±1.34 sec., p=0.0522). Thus, EAAs supplementation resulted in attenuation of muscle atrophy and hastened the time to functional mobility after TKA.

Clinical evidence: studies in THA

In 2017, Aquilani et al examined hip fracture surgery (HFS) cases at an institutional rehabilitation program that might help improve patients' walking performance by achieving +50 meters and whether adding EAAs to the diet may speed up their recovery. Study included 83 elderly subjects (mean age: 79±4.5 years) randomized to receive rehabilitation only (Rehab, N=27); rehabilitation and placebo (RP, N=28) or rehabilitation and EAAs (RE, 8 g/day, n=28).[37] The subjects were administered EAAs packet (4 g) twice daily until discharge. The institutional rehabilitation therapy included passively aided active mobilization of the operated limb twice daily for five days a week, isotonic and isometric exercises, isotonic exercises against resistance, and assisted gait training. At 10±6 days from admission, the patients were evaluated through a 6-Min Walking Distance test (6MWD). At admission, 6MWD was 251±71 m and the test was repeated at discharge (average 60±8 days from admission). At discharge, the walking ability of each group had critical improvement maintaining stable body weight over the rehabilitation period. The average improvement in walking distance in each group exceeded the threshold of clinical significance by +50 meters. While RP did not significantly vary from Rehab, the improvement rate in the RE group was greater compared to RP (pairwise comparison: RE versus RP: p=0.024; RE vs Rehab: p=0.034; RP vs. Rehab: p=0.9). EAA supplementation enhanced the proportion of patients (75%) who achieved +50 m compared to RP (46.4%) and Rehab (66.7%).

In another study, Baldissarro and colleagues enrolled 66 subjects undergoing elective THA and were randomized to EAAs (8 gm/day) or placebo (maltodextrin) for 14 days.[38] These were administered in addition to the institutional rehabilitation protocol. Harris hip score (HHS score) was used to assess hip function. They also included 10 healthy control subjects. All patients of THA had systemic inflammation indicated by elevated C-reactive protein levels (25 times higher than upper limit of normal) and there was severe reduction in hip function (HHS test: 0.78±2.70 scores). In the post-operative rehabilitation period, there was significant functional recovery of hip as indicated by significant change in HHS test in EAA group (41.8±1.15 at admission to 76.37±6.6 at discharge) than placebo (at admission 39.78±4.89 to 70±7.1 at discharge, p=0.006 for comparison between two groups). Thus, supplementation of EAA after THA can augment the functional recovery in addition to rehabilitation protocol. The (Table 1) summarizes the principal findings from these studies.

DISCUSSION

In patients who undergo TKA or THA, muscle deterioration may continue in postoperative period. A meta-analysis of 21 studies identified that in TKA patients, such muscle damage or deterioration continued till 3 to 6 months after TKA than the non-operated leg.[39] Current evidence from randomized trials indicates that EAAs supplementation assists in improving functional recovery, muscle strength and muscle mass in patients undergoing TKA. The administration of EAAs has shown to augment the genes and protein transcription in the muscles leading to increased protein synthesis. This is proven when EAAs are used over and above the rehabilitation alone. A

systematic review of nine studies indicated that EAA supplementation is beneficial in the post-operative period.[15] The muscle strength and functional decline is substantial in the early postoperative period.[18] Thus, targeting the muscle damage as early as possible is necessary. In general, EAAs supplementation has shown to improve the muscle strength and physical function.[40] The optimal protocol for EAAs administration has not been defined accurately. However, from current evidence, we propose that that administration of EAAs 7 to 10 days prior to planned TKA or THA and continued for 14 to 20 days in the postoperative period along with rehabilitation program is optimal in enhancing the muscle strength and help in physical functional recovery.

CONCLUSION

In patients undergoing TKA or THA, essential amino acids (EAAs) are helpful in improving the muscle mass, muscle strength and functional recovery including return to the activities of daily living. Preoperative supplementation is necessary to optimize the recovery in the postoperative period. EAAs should be supplemented in addition to optimal rehabilitation protocol and should be offered to all patients undergoing TKA or THA.

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