근육감소증 조기 진단에 있어서 신경근 접합부 바이오마커, C-말단 아그린 단편(CAF)의 역할: 체계적 고찰 및 메타분석

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The role of Neuromuscular Junction Biomarkers, C-terminal Agrin Fragment (CAF) in Early Diagnosis of Sarcopenia: A Systematic Review and Meta-Analysis

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Abstract

Sarcopenia is a progressive loss of skeletal muscle mass and strength that commonly occurs with aging and chronic diseases. It leads to physical weakness, loss of independence, and an increased risk of falls and mortality. Despite its impact, diagnosing sarcopenia early remains a challenge because existing clinical tools are often costly or unavailable in routine care. This chapter focuses on one biological aspect of sarcopenia — the C-terminal Agrin Fragment (CAF), a circulating marker that reflects the degradation of the neuromuscular junction (NMJ). This research explores how CAF can be used as a biomarker for early detection and monitoring of sarcopenia, summarizing evidence from a systematic review and meta-analysis.

1. Research background

Sarcopenia has emerged as a major health concern in an aging world, affecting nearly half of individuals between 60 and 80 years of age. Traditionally, its diagnosis depends on measurements of muscle mass and strength using MRI, DEXA, or bioelectrical impedance analysis. However, these techniques are expensive, time-consuming, and not easily available in community settings.

Understanding the biological pathways involved in sarcopenia has led to the exploration of blood-based biomarkers. One such promising biomarker is C-terminal Agrin Fragment (CAF). Agrin is a protein essential for maintaining the integrity of the neuromuscular junction — the site where nerves communicate with muscles. With aging and muscle disuse, Agrin is broken down by an enzyme called Neurotrypsin, releasing CAF into the bloodstream.

Elevated CAF levels indicate instability at the NMJ and the early stages of muscle denervation, both of which are central features of sarcopenia. By measuring CAF levels, researchers aim to identify individuals at risk even before noticeable muscle loss occurs.

2. Research methods

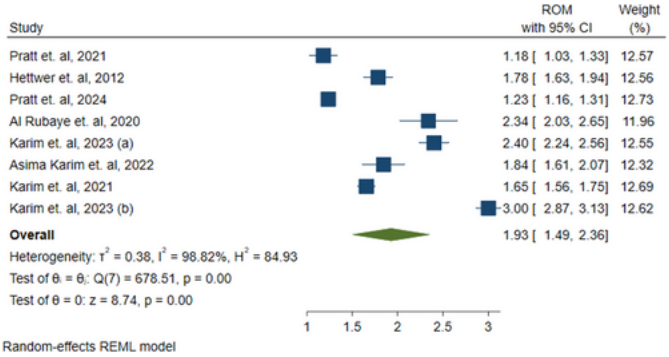
To establish the relationship between CAF and sarcopenia, systematic review and meta-analysis were performed according to PRISMA guidelines. The protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO: CRD42024551517).

Relevant studies published between 2014 and 2024 were retrieved from major databases including PubMed, EMBASE, ISI Web of Science, and the Cochrane Library. Studies were included if they measured CAF concentrations in the blood of sarcopenic and non-sarcopenic individuals aged 50 years or older.

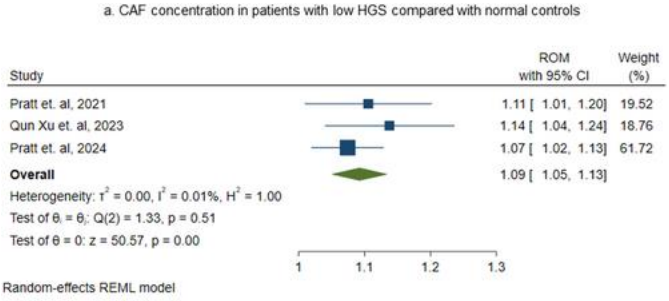
The quality of the studies was assessed using the Joanna Briggs Institute (JBI) Critical Appraisal Tool. Statistical analysis was conducted using STATA software, where the ratio of mean (ROM) was calculated to compare CAF levels between groups. Subgroup, meta-regression, and sensitivity analyses were performed to explore possible sources of heterogeneity, and publication bias was evaluated using funnel plots and Egger's test.

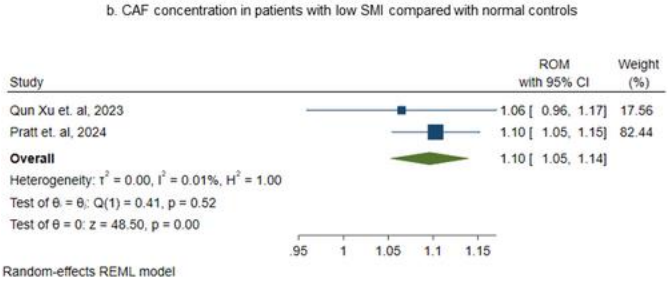
3. Result & conclusion

A total of 17 studies met the inclusion criteria for the review, of which 10 studies were included in the meta-analysis, representing over 3,000 participants worldwide. The results consistently showed that CAF levels were significantly higher in individuals with Sarcopenia compared to those without it. Quantitatively, the effect size indicated that CAF levels were nearly 1.9 times higher in sarcopenic individuals (ROM = 1.93, 95% CI 1.49–2.36).



Moreover, elevated CAF levels were closely associated with reduced handgrip strength (HGS) and lower skeletal muscle index (SMI) two major indicators of muscle function.





Interestingly, although sarcopenia is more prevalent with age, the analysis revealed no significant statistical correlation between CAF levels and chronological age. This suggests that increased CAF concentration is more reflective of neuromuscular degradation rather than aging itself.

All included studies demonstrated a low risk of bias and high methodological quality, strengthening the reliability of the findings.

The findings of this review highlight C-terminal Agrin Fragment (CAF) as a valuable biomarker for identifying and monitoring sarcopenia. Elevated CAF levels strongly correlate with muscle weakness and decreased muscle mass, providing a potential tool for early diagnosis, especially in community or clinical settings where advanced imaging is not available. By offering a simple, blood-based indicator of neuromuscular health, CAF can support preventive strategies, guide rehabilitation programs, and improve outcomes in older adults. Future research should focus on establishing standardized reference ranges and exploring how CAF responds to interventions such as exercise, diet, and pharmacological therapy.

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5. References

1. A. J. Cruz-Jentoft, F. Landi, S. M. Schneider, et al., "Prevalence of and Interventions for Sarcopenia in Ageing Adults: A Systematic Review. Report of the International Sarcopenia Initiative (EWGSOP and IWGS)," *Age and Ageing* **43**, no. 6 (2014): 748–759.

2. E. Marzetti, R. Calvani, M. Lorenzi, et al., "Serum Levels of C-Terminal Agrin Fragment (CAF) Are Associated With Sarcopenia in Older Hip Fractured Patients," *Experimental Gerontology* **60** (2014): 79–82.

3. J. Pratt, G. De Vito, M. Narici, et al., "Plasma C-Terminal Agrin Fragment as an Early Biomarker for Sarcopenia: Results From the GenoFit Study," *Journals of Gerontology: Series A* **76**, no. 12 (2021): 2090–2096.

4. S. Hettwer, P. Dahinden, S. Kucsera, et al., "Elevated Levels of a C-Terminal Agrin Fragment Identifies a New Subset of Sarcopenia Patients," *Experimental Gerontology* **48**, no. 1 (2013): 69–75.

5. M. Drey, C. Sieber, J. Bauer, et al., "C-Terminal Agrin Fragment as a Potential Marker for Sarcopenia Caused by Degeneration of the Neuromuscular Junction," *Experimental Gerontology* **48**, no. 1 (2013): 76–80.