International Journal of Medical Toxicology & Legal Volume 27, No. 4S,
e-ISSN: 0974-4614
p-ISSN: 0972-0448
https://doi.org/10.47059/ijmtlm/V27I4S/148

The role of Growth Differentiation Factor 15 in Acquired Muscle weakness in ICU

Aya Hamdy Ahmed[1], Amany Khairy Abuelhussein[1], Zaki Mohamed Zaki[2], Omyma Shehata Mohamed1

[1]Department of Anesthesia, Intensive Care and Pain Management, Faculty of Medicine, Minia University, Minia, Egypt
[2]Department of Clinical Pathology, Faculty of Medicine, Minia University, Minia, Egypt

Received: 15.09.2024 Revised: 13.10.2024 Accepted: 20.11.2024

ABSTRACT

Background: ICU-acquired weakness (ICU-AW) is a significant problem in very sick patients. It can cause more time on breathing machines, longer hospital stays, and a greater chance of dying. Even though it's important to diagnose it early, it's hard since the typical ways of assessment are limited.
Objective: The current study discusses the relation between Growth Differentiation Factor 15 (GDF-15) and muscle weakness acquired in ICU.
Methods: An analysis was conducted to explore the correlation of plasma GDF 15 level with the incidence of ICUAW and its utility as an early diagnostic biomarker.
Results: High levels of GDF-15 were strongly associated with muscle wasting. Compared to conventional diagnostic methods, GDF-15 has more potential to identify and predict ICU-AW in an early phase.
Conclusion: GDF-15 holds great promise as a biomarker for ICU-AW, offering valuable help in early diagnosis and treatment. Its clinical applications and the modes of treatments associated with GDF-15 need further studies to bring down muscle losses in critically ill patients.

Keywords: ICU-acquired weakness, Growth Differentiation Factor 15, muscle atrophy, biomarker, critical illness, prognosis.

INTRODUCTION

Muscle weakness is a prevalent issue in the intensive care unit (ICU). Acute care is necessitated for primary neuromuscular disorders, including Guillain-Barré Syndrome, myasthenia gravis, amyotrophic lateral sclerosis, and multiple sclerosis, which can induce weakness, nonetheless these ailments represent merely 0.5% of total ICU admissions[1].
Muscle weakness often arises as a secondary symptom in patients undergoing treatment for other life- threatening ailments.Intensive care unit-acquired muscle weakness indicates that this neuromuscular impairment is solely attributable to the critical illness and its related treatments [2].

Risk Factors

Numerous independent risk factors for the onset of ICU-acquired muscular weakness have been found, primarily through observational research, albeit frequently not definitively[3].

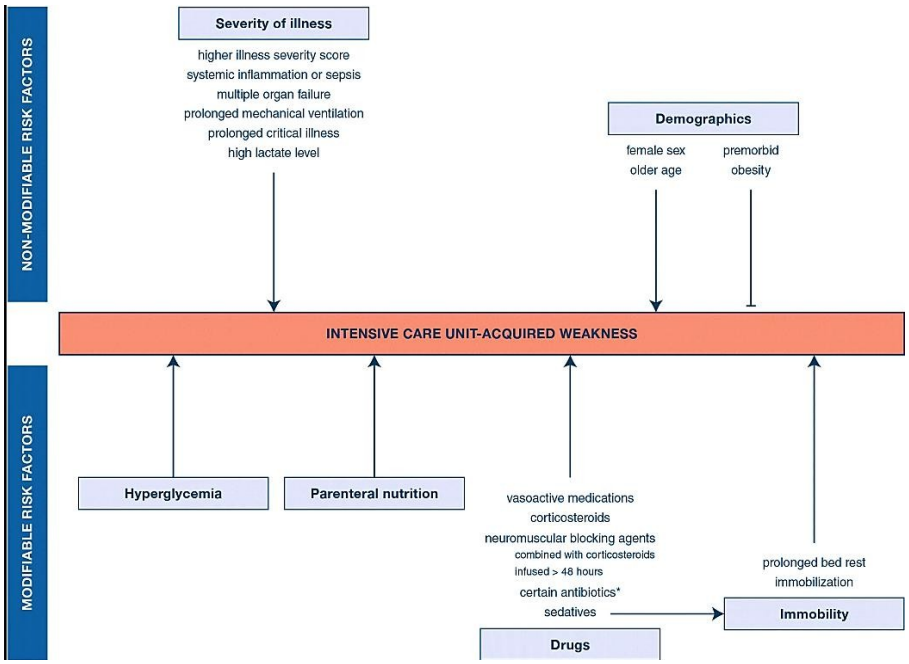

Figure 1: Overview of risk factors of ICU-acquired weakness[3].

Not modifiable risk factors:

One critical risk factor is the severity of acute illness. The severity of illness, the occurrence of sepsis and inflammation, the existence of multiple organ failure, and the duration of mechanical ventilation and intensive care unit stay were identified as predictive factors [4].

Patients who are critically ill for prolonged durations are more susceptible to developing weaknesses while in the intensive care unit [5].

1. Multiple Organ Failure
2. Mobility Restriction

Modifiable risk factors

Various medications administered to critically sick patients can influence the extent of hyperglycemia induced by the extreme stress of critical illness and the provision of parenteral nourishment [6]. The likelihood of acquiring muscle weakness in the intensive care unit (ICU) escalates with the dosage and duration of vasoactive medicines, particularly –agonists [4].

ICU-acquired weakness has been associated with corticosteroid administration in meta-analyses encompassing diverse patient cohorts, including those with sepsis. Nonetheless, one study indicated that preventing hyperglycemia during corticosteroid treatment may confer a protective effect [3].

1. Hyperglycemia
2. Glucocorticoids
3. Pathophysiology
4. Critical illness myopathy (CIM)
5. Reduced muscle mass (Muscle atrophy or wasting)
6. Reduced Muscle function (Contractile Impairment)
7. Critical illness polyneuropathy (CIP)

Clinical Manifestations

The primary characteristics include symmetrical and flaccid weakness of limb muscles, more pronounced in proximal than distal muscles, together with weakness of respiratory muscles, leading to challenges in weaning from mechanical breathing. "Ventilator-induced diaphragmatic dysfunction" (VIDD) denotes the early and time- dependent onset of diaphragmatic atrophy and weakening [7].

Diagnosis

Multiple methodologies are employed to identify ICU-acquired muscle weakness. These techniques evaluate peripheral and/or respiratory muscle strength.

Assessment of peripheral muscle strength

A clinical assessment of muscle strength is essential for diagnosing ICU-acquired muscle weakness.

1. Volitional functional testing [8].
2. Electrophysiological testing [9].
3. Imaging and others [10].

Treatment of ICU-AW

The management of ICU-AW mostly relies on prevention, as there is still no effective treatment available. Consequently, it is crucial to prevent or address infection and inflammation promptly to mitigate the risk of ICU-acquired weakness (ICU-AW). Timely intervention for sepsis can avert the onset of muscle damage caused directly and indirectly by inflammation and facilitate the prompt restoration of physical function, hence diminishing the prevalence of muscular weakness [11].
Tight glycemic control may prevent ICU-AW, but it carries significant dangers; research indicates an elevated mortality risk associated with stringent glucose management, probably related to hypoglycemia. The ideal glucose levels are still debated; nevertheless, evidence from multicenter randomized controlled trials indicates that moderate blood glucose levels may be safer [12].

Biomarkers in diagnosis of muscle weakness acquired in ICU

The use of biomarkers could allow better targeting of future novel therapies. Creatine kinase may be increased in patients with ICUAW but is not a good biomarker. Plasma levels of neurofilaments, which are biomarkers of axonal injury, are also elevated in patients with ICUAW. Peak neurofilament levels showed good discriminative power for weakness but this peak only occurred after patients were clinically evaluable and therefore did not allow early diagnosis. Although no validated biomarkers are available currently, identification of new mediators involved in the development of ICU-AW, such as GDF-15, may represent promising future candidates [13].

Growth differentiation factor-15 (GDF-15)

Growth differentiation factor-15 (GDF-15) is a transforming growth factor (TGF-) protein associated with the pathogenesis of various diseases, including muscle atrophy, chronic obstructive pulmonary disease (COPD), cancer, and pulmonary hypertension [14].
GDF15 was initially identified as macrophage inhibitory cytokine-1 (MIC) in 1990. GDF15 is a member of the transforming growth factor-beta (TGF-β) superfamily and is considered a stress-response component of TGF-β. GDF15 is encoded by human chromosome 19p13.11-13.2, which was cloned in 1997 by macrophage activation. GDF15 is generally present in low concentrations, except in the placenta, where it is substantially expressed during pregnancy. GDF15 levels are elevated during pregnancy and after organ injury, particularly in the lungs and liver. Under physiological settings, it is predominantly expressed by adipocytes, skeletal muscle, smooth muscle, cardiac muscle cells, and macrophages [15].

The function of GDF 15 in several pathologies

The precise function of GDF15 is not fully understood; however, it is crucial in regulating cell proliferation, apoptosis, and inflammatory activity. Thus, GDF15 is recognized as a predictive biomarker in oncology, inflammatory disorders, and cardiovascular problems. GDF15 is overexpressed in multiple cancer cell types, including renal, prostatic, colorectal, urothelial, and melanoma. GDF15 induces weight loss by suppressing appetite; hence, neutralizing antibodies against GDF15 may mitigate cancer-induced cachexia [16].
Moreover, GDF15 may function as both an anti-inflammatory and pro-inflammatory signal in many cardiovascular problems. The p53 protein has been demonstrated to enhance the production of GDF15 during inflammation and oxidative stress. Moreover, the secretion of GDF15 is stimulated by several growth factors and cytokines, including TGF-β, tumor necrosis factor (TNF)-α, interleukin-1β (IL-1β), macrophage colony- stimulating factor (M-CSF), angiotensin II (AngII), and p53 (Figure (3)). Moreover, endoplasmic reticulum stress was considered a crucial role in the production of macrophage GDF1 due to the saturation of free fatty acids and the activation of the unfolded protein response. These data indicate that GDF1 expression occurs in several cell types under both healthy and pathological situations [17].

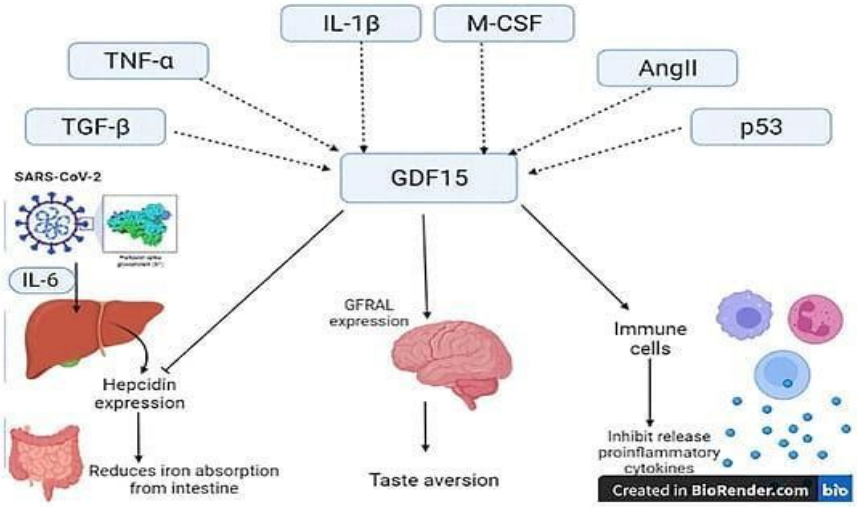

Figure 3: Activation of growth differentiation factor 15 (GDF15) and its action [18].

GDF15 is activated by TGF-β (transforming growth factor-β), TNF-α (tumor necrosis factor-α), IL (interleukin)-1β, M-CSF (macrophage colony-stimulating factor), AngII (angiotensin II) and p53. GDF15 stimulates immune cells and activates glial-derived neurotrophic factor family receptor α-like (GFRAL) in the brain. In addition, GDF15 counteracts hepcidin which increased in various viral infections including SARS- CoV-2 due to the elevation of IL-6 [18].

GDF15 is associated with the progression of many cardiometabolic diseases and cancer. Recent research indicates that GDF15 is classified as a cytokine with anti-inflammatory properties that enhances insulin sensitivity, potentially reducing body weight and improving clinical outcomes in diabetic patients. In healthy individuals, elevated GDF15 expression diminishes hunger and inflammation while enhancing insulin sensitivity. In chronic metabolic and inflammatory illnesses, the overexpression of GDF15 may lead to desensitization of central and peripheral GDF15 receptors, resulting in elevated serum levels of GDF15 [17].

Additionally, GDF15 levels have been observed to elevate in numerous cardiometabolic and inflammatory conditions, such as heart failure and rheumatoid arthritis. A systematic analysis encompassing 21 clinical investigations demonstrated that GDF15 serum levels are considered a novel biomarker for heart failure [19].

A prospective study involving 46 patients with rheumatoid arthritis and 36 matched healthy controls demonstrated that serum levels of GDF15 were elevated in rheumatoid arthritis patients compared to the controls [20].

GDF15 stimulates the glial-derived neurotrophic factor family receptor α-like (GFRAL), which is prominently expressed in the brain stem, to produce taste aversion. The GFRAL receptors facilitate the metabolic effects of GDF15. Dysregulation in the expression and sensitivity of GFRAL receptors may be involved in the etiology of diabetes mellitus and obesity [21].

The serum level of GDF15 is associated with the severity of COVID-19. A small prospective study with 58 COVID-19 survivors and 8 non-survivors indicated that elevated serum GDF15 levels correlated with increased mortality [22]. Ahmed et al. established that elevated GDF15 serum levels serve as a predictive biomarker and are associated with the severity of COVID-19 [23]. Teng et al. noted that fluctuations in GDF15 serum levels are associated with the advancement of SARS-CoV-2 infection and may serve as a marker for COVID-19 severity. Consequently, GDF15 serum levels may serve as a potential diagnostic and prognostic biomarker in critically ill COVID-19 patients [24].

GDF-15 and Skeletal Muscle

Elevated GDF-15 levels have been noted in many clinical diseases when muscle function is compromised, as a component of tissue stress responses. The impact of GDF-15 induction on muscle tissue repair remains ambiguous, whether it is predominantly advantageous or harmful. A direct catabolic effect on mouse skeletal muscle cells has been demonstrated both in vivo (Patel et al., 2019[25]) and in vitro (Patsalos et al., 2021[26]).

GDF-15 seems to induce fibrotic alterations mediated by the TGF-β pathway through the downregulation of muscle-protective microRNAs. Nonetheless, a beneficial impact of GDF-15 on myoblast proliferation has been proposed, facilitated by the activation of regeneration-enhancing processes in macrophages [26].
GDF-15 is co-expressed with established muscle regeneration-associated growth factors under the regulation of peroxisome proliferator-activated receptor γ (PPARγ) and retinoid X receptor α (RXRα), and is preferentially expressed in a subset of macrophages that participate in muscle repair. The conflicting actions of the same cytokine may be elucidated by advantageous effects driven by cell-specific and timely production, which could activate distinct processes in contrast to those induced by systemic overexpression. Chronically raised circulating GDF-15 levels induce detrimental effects on growth and metabolism and are associated with an increased risk of all-cause death [27].

Sarcopenia

GDF-15, a cytokine generated by stress, is regarded as a biomarker of biological age. In aging, compromised mitochondrial activity is a significantly correlated process, leading to the accumulation of reactive oxygen species and ensuing oxidative stress-induced tissue damage. Although gradual increases in circulation GDF-15 with age may not be detrimental, significant elevations of GDF-15 negatively impact muscle mass and correlate with reduced muscular strength [28].
In mouse models, elevated serum and muscle concentrations of GDF-15 in aged mice result in diminished food consumption, weight reduction, and decreased skeletal muscle mass and functionality [29].
The muscle tissue itself actively facilitates the increase of circulating GDF-15. Murine myotube cultures can be induced to synthesize GDF-15 using oxidative and endoplasmic reticulum stresses that replicate age-associated stress [30]. Although a strong and constant correlation between GDF-15 and muscle catabolism is shown in animal studies, this is less pronounced in human investigations. Certain studies associate sarcopenia, frailty, and diminished physical performance in elderly individuals with elevated circulating GDF-15 levels [31], while other research indicates gender-specific variations or fails to identify a correlation [32], and some findings suggest that GDF-15 levels do not serve as predictors of sarcopenia [33].

Mitochondrial Myopathy

GDF-15 blood concentrations seem to be especially valuable in diagnosing early-onset mitochondrial myopathy and in detecting mtDNA deletions and translation abnormalities. Muscle cells impacted by mitochondrial diseases actively produce and secrete GDF-15 [34], leading to increased cytokine levels in patients. Serum GDF- 15 exhibited remarkable diagnostic sensitivity and specificity approaching 100%, with an AUC of 0.997 in a cohort of 48 patients diagnosed with mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS), Leigh syndrome, or Kearns-Sayre syndrome (KSS) [35]. Serum GDF-15 exhibited a sensitivity of 70%, specificity of 90%, and an AUC of 0.82 in a varied cohort of 16 individuals with molecularly proven mitochondrial diseases. Serum GDF-15 levels were elevated in patients with TK2 abnormalities, MELAS, MT- TL1 deficiencies encoding mitochondrial tRNA leucine, as well as in those with Pearson syndrome and Kearns- Sayre syndrome [36].

Weakness acquired in the Intensive Care Unit

GDF-15, a cytokine, is a crucial regulator of the equilibrium between protein synthesis and catabolism and may participate in the activation of proteolytic pathways [37]. Overexpression in the human body can diminish muscle protein synthesis and induce muscular atrophy [38].
In the study by Xie et al., the GDF-15 level in the ICU-AW group was markedly elevated compared to the non- ICU-AW group until the seventh day [38]. A bedside ultrasound examination concurrently indicated a considerable reduction in the cross-sectional area of the patient's left rectus femoris muscle. The findings indicated that ICU-AW patients experienced considerable acute skeletal muscle atrophy [38].
Bloch et al. found that GDF-15 levels were increased in high-risk patients following cardiac surgery in the ICU. Subsequently, they conducted in vitro tests to verify that GDF-15 induces myotube atrophy. Moreover, their research revealed that GDF-15 can suppress muscle miRNA expression and facilitate muscle atrophy by enhancing the sensitivity of TGF- signaling. This conclusion was derived from the examination of muscle biopsies of the rectus femoris in patients with ICU-acquired weakness [39].
GDF-15 has been identified as an effective biomarker for muscular atrophy, demonstrating a strong connection with bedside ultrasonography assessments of rectus femoris muscle mass reduction. Xie et al. [38] evaluate the magnitude of muscular atrophy in ICU-AW patients collaboratively. Additionally, they are associated with the MRC score, which indicates the patient's muscular function. Consequently, they might enhance one another and cooperate. The plasma GDF-15 level and RFcsa loss may facilitate the early diagnosis of ICU-AW in patients, especially those in a coma or under

sedation, where the MRC muscle strength score is unassessable [38].

Xie et al. (2020) [38] found that elevated plasma GDF-15 levels on the seventh day correlate with reduced 90-day survival rates in mechanically ventilated ICU patients, aligning with increased mortality in critically ill patients diagnosed with ICU-AW [40].
This also demonstrated that ICU-AW adversely affects the quality of life and prognosis of critically ill patients. The discussion indicated that the prolonged ventilation time in ICU-AW patients may stem from their weakened respiratory muscles, thereby elevating the risk of problems such as ventilator-associated pneumonia and the failure rate of tracheal intubation extubation [41]. Moreover, limb weakness prolongs the patient's bed rest, resulting in difficulties associated with being bedridden [42].
Xie et al.[38] determined that the persistent increase in plasma GDF-15 concentration is substantially correlated with skeletal muscle function and muscle atrophy in ICU patients undergoing mechanical ventilation. The plasma GDF-15 level on the seventh day exhibits a significant diagnostic yield for ICU-acquired muscular weakness and is identified as a "ideal" potential biomarker for muscle mass depletion in ICU-AW patients. A consistently high plasma GDF-15 concentration indicates a potentially adverse prognosis, and the plasma GDF- 15 level on the seventh day can forecast the 90-day survival outcome of mechanically ventilated ICU patients.

CONCLUSION

ICU-acquired weakness (ICU-AW) is a serious problem in severely ill patients. It may result in prolonged time on a ventilator, longer ICU stay, and greater death. Growth differentiation factor 15 (GDF-15) has been found to be a valuable marker for diagnosis and prognosis of ICU-AW. It is strongly linked with muscle wasting and adverse outcomes.
As a TGF-β family stress-response cytokine, GDF-15 plays a role in muscle wasting, inflammation, and metabolic stress. Studies show that chronically elevated GDF-15 levels lead to muscle wasting and are also predictive of decreased ICU survival. In contrast to traditional diagnostic approaches, GDF-15 offers early detection and prognostic value, and as a result, is a more suitable biomarker for ICU-AW.
Despite the promise, more research is required to establish reference levels and explore therapeutic targeting. In conclusion, GDF-15 is an effective marker for the diagnosis and prognosis of ICU-AW early. Its introduction into clinical practice can help improve patient management, but more validation is needed in order to achieve maximum usefulness and develop targeted interventions.

REFERENCES

1. Damian, M. S., & Wijdicks, E. F. (2019). The clinical management of neuromuscular disorders in intensive care. Neuromuscular Disorders, 29(2), 85-96.
2. Wang, W., Xu, C., Ma, X., Zhang, X., & Xie, P. (2020). Intensive care unit-acquired weakness: a review of recent progress with a look toward the future. Frontiers in medicine, 7, 559789.
3. Vanhorebeek, I., Latronico, N., & Van den Berghe, G. (2020). ICU-acquired weakness. Intensive care medicine, 46(4), 637-653.
4. Wolfe, K. S., Patel, B. K., MacKenzie, E. L., Giovanni, S. P., Pohlman, A. S., Churpek, M. M., . . . Kress, J. P. (2018). Impact of vasoactive medications on ICU-acquired weakness in mechanically ventilated patients. Chest, 154(4), 781-787.
5. Latronico, N. (2016). Critical illness polyneuropathy and myopathy 20 years later. No man’s land? No, it is our land! Intensive care medicine, 42(11), 1790-1793.
6. Yang, T., Li, Z., Jiang, L., Wang, Y., & Xi, X. (2018). Risk factors for intensive care unit-acquired weakness: a systematic review and meta-analysis. Acta Neurologica Scandinavica, 138(2), 104-114.
7. Jaber, S., Jung, B., Matecki, S., & Petrof, B. J. (2011). Clinical review: Ventilator-induced diaphragmatic dysfunction-human studies confirm animal model findings! Critical care, 15(1), 1-8.
8. Roberson, A. R., Starkweather, A., Grossman, C., Acevedo, E., & Salyer, J. (2018). Influence of muscle strength on early mobility in critically ill adult patients: systematic literature review. Heart & Lung, 47(1), 1-9.
9. Kelmenson, D. A., Quan, D., & Moss, M. (2018). What is the diagnostic accuracy of single nerve conduction studies and muscle ultrasound to identify critical illness polyneuromyopathy: a prospective cohort study. Critical care, 22(1), 1-9.
10. Joskova, V., Patkova, A., Havel, E., Najpaverova, S., Uramova, D., Kovarik, M., . . . Hronek, M. (2018). Critical evaluation of muscle mass loss as a prognostic marker of morbidity in critically ill patients and methods for its determination. Journal of rehabilitation medicine, 50(8), 696-704.
11. Farhan, H., Moreno-Duarte, I., Latronico, N., Zafonte, R., & Eikermann, M. (2016). Acquired muscle weakness in the surgical intensive care unit: nosology, epidemiology, diagnosis, and prevention. Anesthesiology, 124(1), 207-234.
12. Norton, R. (2012). Hypoglycemia and risk of death in critically ill patients. New England Journal of Medicine, 367(12).

13. Wieske, L., Witteveen, E., Petzold, A., Verhamme, C., Schultz, M. J., van Schaik, I. N., & Horn, J. (2014). Neurofilaments as a plasma biomarker for ICU-acquired weakness: an observational pilot study. Critical care, 18(1), 1-9.
14. Desmedt, S., Desmedt, V., De Vos, L., Delanghe, J. R., Speeckaert, R., & Speeckaert, M. M. (2019). Growth differentiation factor 15: A novel biomarker with high clinical potential. Critical Reviews in Clinical Laboratory Sciences, 56(5), 333-350.
15. Wollert, K. C., Kempf, T., & Wallentin, L. (2017). Growth differentiation factor 15 as a biomarker in cardiovascular disease. Clinical chemistry, 63(1), 140-151.
16. Wu, Z., Bennett, D., Brosnan, J., Calle, R., Collins, S., Esquejo, R., . . . LaCarubba, B. (2020). 2O growth differentiation factor 15 (GDF-15) neutralization reverses cancer cachexia, restores physical performance and mitigates emesis associated with platinum-based chemotherapy. Annals of Oncology, 31, S245.
17. Eddy, A. C., & Trask, A. J. (2021). Growth differentiation factor-15 and its role in diabetes and cardiovascular disease. Cytokine & growth factor reviews, 57, 11-18.
18. Babalghith, A. O., Al-Kuraishy, H. M., Al-Gareeb, A. I., De Waard, M., Sabatier, J.-M., Saad, H. M., & Batiha, G. E.-S. (2022). The potential role of growth differentiation factor 15 in COVID-19: a corollary subjective effect or not? Diagnostics, 12(9), 2051.
19. George, M., Jena, A., Srivatsan, V., Muthukumar, R., & Dhandapani, V. (2016). GDF 15-a novel biomarker in the offing for heart failure. Current cardiology reviews, 12(1), 37-46.
20. Tanrıkulu, O., Sarıyıldız, M. A., Batmaz, İ., Yazmalar, L., Polat, N., Kaplan, İ., & Çevik, R. (2017). Serum GDF-15 level in rheumatoid arthritis: relationship with disease activity and subclinical atherosclerosis. Acta reumatologica portuguesa(1).
21. Rochette, L., Zeller, M., Cottin, Y., & Vergely, C. (2020). Insights into mechanisms of GDF15 and receptor GFRAL: therapeutic targets. Trends in Endocrinology & Metabolism, 31(12), 939-951.
22. de Guadiana Romualdo, L. G., Mulero, M. D. R., Olivo, M. H., Rojas, C. R., Arenas, V. R., Morales, M. G., . . . Hernández, A. C. (2021). Circulating levels of GDF-15 and calprotectin for prediction of in-hospital mortality in COVID-19 patients: A case series. Journal of Infection, 82(2), e40-e42.
23. Ahmed, D. S., Isnard, S., Berini, C., Lin, J., Routy, J.-P., & Royston, L. (2022). Coping with stress: the mitokine GDF-15 as a biomarker of COVID-19 severity. Frontiers in immunology, 13, 820350.
24. Teng, X., Zhang, J., Shi, Y., Liu, Y., Yang, Y., He, J., . . . Liu, D. (2021). Comprehensive profiling of inflammatory factors revealed that growth differentiation factor-15 is an indicator of disease severity in COVID-19 patients. Frontiers in immunology, 12, 662465.
25. Patel, S., Alvarez-Guaita, A., Melvin, A., Rimmington, D., Dattilo, A., Miedzybrodzka, E. L., . . . Meek, C. L. (2019). GDF15 provides an endocrine signal of nutritional stress in mice and humans. Cell metabolism, 29(3), 707-718. e708.
26. Patsalos, A., Halasz, L., Medina-Serpas, M. A., Berger, W. K., Daniel, B., Tzerpos, P., . . . Simandi, Z. (2021). A growth factor–expressing macrophage subpopulation orchestrates regenerative inflammation via GDF-15. Journal of Experimental Medicine, 219(1), e20210420.
27. Wiklund, F. E., Bennet, A. M., Magnusson, P. K., Eriksson, U. K., Lindmark, F., Wu, L., . . . Pedersen, N.
L. (2010). Macrophage inhibitory cytokine-1 (MIC-1/GDF15): a new marker of all-cause mortality. Aging cell, 9(6), 1057-1064.
28. Alcazar, J., Frandsen, U., Prokhorova, T., Kamper, R. S., Haddock, B., Aagaard, P., & Suetta, C. (2021). Changes in systemic GDF15 across the adult lifespan and their impact on maximal muscle power: the Copenhagen Sarcopenia Study. Journal of cachexia, sarcopenia and muscle, 12(6), 1418-1427.
29. Kim, H., Kim, K. M., Kang, M. J., & Lim, S. (2020). Growth differentiation factor-15 as a biomarker for sarcopenia in aging humans and mice. Experimental Gerontology, 142, 111115.
30. Ito, T., Nakanishi, Y., Yamaji, N., Murakami, S., & Schaffer, S. W. (2018). Induction of growth differentiation factor 15 in skeletal muscle of old taurine transporter knockout mouse. Biological and Pharmaceutical Bulletin, 41(3), 435-439.
31. Arauna, D., García, F., Rodríguez-Mañas, L., Marrugat, J., Sáez, C., Alarcón, M., . . . Fuentes, E. (2020). Older adults with frailty syndrome present an altered platelet function and an increased level of circulating oxidative stress and mitochondrial dysfunction biomarker GDF-15. Free Radical Biology and Medicine, 149, 64-71.
32. Nga, H. T., Jang, I.-Y., Kim, D. A., Park, S. J., Lee, J. Y., Lee, S., . . . Lee, Y.-H. (2021). Serum GDF15 level is independent of sarcopenia in older Asian adults. Gerontology, 67(5), 525-531.
33. Kim, M., Walston, J. D., & Won, C. W. (2022). Associations between elevated growth differentiation factor-15 and sarcopenia among community-dwelling older adults. The Journals of Gerontology: Series A, 77(4), 770-780.
34. Ost, M., Igual Gil, C., Coleman, V., Keipert, S., Efstathiou, S., Vidic, V., . . . Klaus, S. (2020). Muscle-derived GDF15 drives diurnal anorexia and systemic metabolic remodeling during

mitochondrial stress. EMBO reports, 21(3), e48804.
35. Yatsuga, S., Fujita, Y., Ishii, A., Fukumoto, Y., Arahata, H., Kakuma, T., . . . Saiki, R. (2015). Growth differentiation factor 15 as a useful biomarker for mitochondrial disorders. Annals of neurology, 78(5), 814-823.
36. Montero, R., Yubero, D., Villarroya, J., Henares, D., Jou, C., Rodríguez, M. A., . . . Campistol, J. (2016). GDF-15 is elevated in children with mitochondrial diseases and is induced by mitochondrial dysfunction. PloS one, 11(2), e0148709.
37. Hofmann, M., Schober-Halper, B., Oesen, S., Franzke, B., Tschan, H., Bachl, N., . . . Wessner, B. (2016). Effects of elastic band resistance training and nutritional supplementation on muscle quality and circulating muscle growth and degradation factors of institutionalized elderly women: the Vienna Active Ageing Study (VAAS). European journal of applied physiology, 116, 885-897.
38. Xie, Y., Liu, S., Zheng, H., Cao, L., Liu, K., & Li, X. (2020). Utility of plasma GDF-15 for diagnosis and prognosis assessment of ICU-acquired weakness in mechanically ventilated patients: prospective observational study. BioMed Research International, 2020.
39. Bloch, S., Lee, J., Syburra, T., Rosendahl, U., Griffiths, M., Kemp, P., & Polkey, M. (2015). Increased expression of GDF-15 may mediate ICU-acquired weakness by down-regulating muscle microRNAs. Thorax, 70(3), 219-228.
40. Witteveen, E., Wieske, L., Sommers, J., Spijkstra, J.-J., de Waard, M. C., Endeman, H., . . . Verhamme, C. (2020). Early prediction of intensive care unit–acquired weakness: a Multicenter External Validation Study. Journal of Intensive Care Medicine, 35(6), 595-605.
41. Verceles, A. C., Wells, C. L., Sorkin, J. D., Terrin, M. L., Beans, J., Jenkins, T., & Goldberg, A. P. (2018). A multimodal rehabilitation program for patients with ICU acquired weakness improves ventilator weaning and discharge home. Journal of critical care, 47, 204-210.
42. Hermans, G., & Van den Berghe, G. (2015). Clinical review: intensive care unit acquired weakness. Critical care, 19(1), 1-9.