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Editorial

Endothelin-1, A Key Player in Sarcopenia?

Orlando Angulo*

Sports Medicine and Sports Nutrition Department, Renacera IPS, Colombia

***Corresponding Author:** Orlando Angulo, Sports Medicine and Sports Nutrition Department, Renacera IPS, Colombia.

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It is well known that quality and quantity of muscle mass decline with ageing. This decline known as sarcopenia also affects endothelial function and it is associated with chronic diseases and unhealthy lifestyle [14].

Sarcopenia definition

It was first mentioned by Rosemberg [13] and Delmonico defined it as: a syndrome characterized by the progressive and widespread loss of skeletal muscle mass and strength with increased risk of physical disability, chronic non-transmissible diseases, reduced quality of life and death [12]. It was even mentioned in 2014 by Angulo., et al. [15], the concept of biochemical sarcopenia, where two out of four biochemical markers (HGH, IGF-1, estradiol, cortisol, testosterone) affected meant already the presence of the condition.

The European consensus [14]:

1. Muscle mass loss: presarcopenia.
2. Muscle mass loss + low strength: Sarcopenia.
3. Muscle mass loss + low strength + low performance: severe sarcopenia.

Position of the Colombian society of Sarcopenia [5].

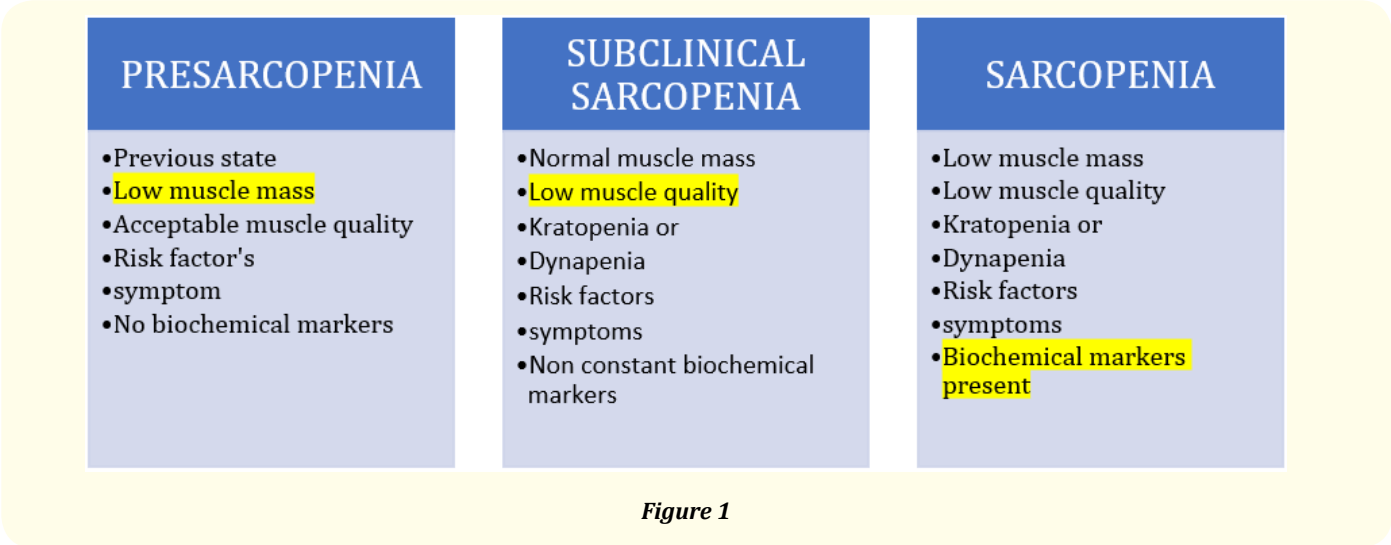

Figure 1

Relationship endothelium and muscle

Recent evidence speaks of the relationship among Sarcopenia, endothelium dysfunction and insulin resistance [6]. As we age the capacity of protein synthesis diminishes and muscle breakdown increases, not only that is troublesome for muscle homeostasis but the fact that muscle tissue needs a good and stable blood flow plays a role to take into account. The latter is also affected by aging, one rodent study by Lemarie., *et al*. showed the dysregulation of EPCs and inhibition of the gene SIRT1 as a role in the development of endothelial dysfunction [16]. Others have shown Nos receptor uncoupling, ROS elevation and increased inflammation [17].

Endothelin system

The endothelins are proteins with vasoconstrictive characteristics that play different roles in the vascularity and other organs. They were showed for the 1st time in 1985 (Hickey., *et al*.) as a constrictor peptide produced by the endothelium [1]. Three years later it was cloned and Isolated (Yanagisawa., *et al*.) and found to be a 21 aminoacids peptides with vasoconstrictive properties [1,2]. ET-1 is the predominant and has inotropic and mitogenic properties, stimulates the RAAS influencing the Salt and water homeostasis [2]. Endothelin is secreted by the endothelial cells and acts in an autocrine and paracrine manner and can be stimulated by: hormones, peptides, xenobiotics, physico-chemical stimuli, blood components and inhibited by: Prostacyclin, NO, PPARY, etc [1,2].

Endothelin synthesis starts by: preproEt-1 genes which will be translated to preproET mRNA which later on will give place to the PreproEt-1 (212aa). This one will become Big ET-1 mediated by Furin-like enzyme. In the end the Big Et-1 will be converted to ET-1 through the action of ECE (Endothelin converting enzymes) in its two variants (ECE-1 and ECE-2) [1,2].

Endothelins comes as a result of cleaving from PreproET-1 and the outcome is 4 isoforms (ET-1, 2, 3 and 4) [3].

Endothelins are produced in endothelial cells but can also be produced in the heart, kidney, posterior pituitary and CNS as well [2].

ET-1

ET-1 is produced by endothelial cells, fibroblasts, macrophages, epithelial cells, VSMC, pancreatic islets, cardiac myocytes, brain neurons [4].

ET-1 binds to ET-A and ET-B receptor on VSMC producing vasoconstriction, proliferative and hypertrophic action, also is pro-inflammatory, produces fibrosis and it is mitogenic which are important in terms of vascular tone and remodeling [1,3]. ET-1 is stimulated by angiotensin II, thrombin, vasopressin, cytokines, epinephrine, hypoxia, insulin and growth factors [1].

ET-A receptor is predominant in the aorta but it is also expressed in heart, kidneys, liver, neurons, osteoblasts, melanocytes, keratinocytes, adipocytes and reproductive system [1,3]. When ET-1 binds the ET-A receptor in the aorta it exerts a vasoconstrictive action [1]. It seems to play a role in maintaining vascular tone and blood pressure [1,2]. Et-A receptors are found to be upregulated by NO and insulin in VSMC [3]. It has been show that when a blocking of either ET-1 or ET-A in mice the outcome is a raised in blood pressure due to a hypoxia produced by craniofacial developmental deformities that disturb respiration and some of these are alike to those of the Pierre Robin syndrome; furthermore, mutations in the ET-B receptor gene have been found in Hirschprung´s disease [1].

ET-B are found more in pulmonary vessels and veins than in arteries [1]. ET-B are also found in the endothelium and produces vasodilation through the production of NO and prostacyclin [1,2].

They have been also identified in mesenteric arteries, human mammary arteries, aorta, coronary arteries, neurons, brainstem glia, renal tubules, multiple endocrine tissues, reproductive tract, osteoblast, airway smooth muscle cells, collecting duct epithelial cells [4].

It has been reported that there are only few ET-B receptors in the coronary arteries, which make ET-1 effect on coronaries basically vasoconstrictive. There are two subtypes ET-B1 and ET-B2; however, their molecular basis is still not well known [3]. The ET-B receptor exerts and inhibitory effect on cell growth and vasoconstriction [4]. Moreover, it functions as a clearance receptor, being this very important in lungs where it clears the ET-1 in a 80% [4].

It has been shown that ET-1 via ET-B receptor may mediate a role in inhibition of sodium and water reabsorption. ET-B receptors are found to be upregulated by TNF-α and bFGF.

ET-1 interferes with the insulin signaling leading to an insulin resistance [9] where the ETAR along with ET-1 will inhibit insulin-induced Akt phosphorylation plus [3H]2-DG uptake depending in a Gq/11 protein- and GRK2 manner in skeletal muscle tissue; thus, ridding the vessel not only of the vasodilatation effect but to its anabolic effect which in the end helps to maintain protein synthesis and the anabolic state above the catabolic one.

When we speak of skeletal muscle anabolism it comes to our minds the AKT and mTOR signaling right away. Question is, does ET-1 have any effect on this?

Well in a rodent study by Takahiro Horinouchi., *et al.* they used rat L6 skeletal muscle cell successfully differentiated into myotubes and found that ET-1 suppressed insulin-induced Akt phosphorylation at Thr(308) and Ser(473) and [(3)H]2-DG uptake in a GRK2-dependent manner in skeletal muscle cells via ETA receptors [7].

In terms of sarcopenia pathophysiology, we know the increase in protein breakdown, decrease in protein synthesis, Ca reuptake dysregulation un muscle cell by the RER, mitochondrial DNA damage and affection to motor neurons. Regarding the latter it has been published the implication of ET-1 in ALS, where it affects the motor neurons via the Nitric Oxide and PI3K/Akt Pathway [8].

Now again do we have a relationship between ET-1 and Skeletal muscle? well we have to say that they do not get along that much, it is a very difficult relationship. Nonetheless and as in any couple there is always a way out of the trouble. Equilibrium balance the endless homeostasis in any human being.

So how can we target and ease this tormented and hateful relationship between the ET-1 signaling and the skeletal muscle tissue. Well indeed we can from the pharmacologic point of view till the healthy lifestyle including physical activity point of view [6,9-11].

Further research is needed regarding the impact of assessment and outcome when targeting muscle quantity and quality from improving endothelial function which in the end would be an anti-aging treatment.

More importantly than saving lives, it is improving lives. In the end life is supposed to get to an end; so as long as we have a life, let us live it well and with quality for us and for those who surround us.

Bibliography

1. Ernesto L Schiffrin. "Vascular endothelin in hypertension". *Vascular Pharmacology* 43.1 (2005): 19-29.

2. William G., *et al.* "Endothelin as a regulator of cardiovascular function in health and disease". *Journal of Hypertension* 16.8 (1998): 1081-1098.

3. Meri M Hynynen. "The vascular endothelin system in hypertension--recent patents and discoveries". *Recent Patents on Cardiovascular Drug Discovery* 1.1 (2006): 95-108.

4. Juan Carlos Galvis MD. "Endothelin: 20 year from discovery to therapy". *Canadian Journal of Physiology and Pharmacology* 86.8 (2008): 485-498.

5. Colombian Sarcopenia Society position stand.

6. Kyle L Timmerman and Elena Volp. "Endothelial Function and the Regulation of Muscle Protein Anabolism in Older Adults". *Nutrition, Metabolism and Cardiovascular Diseases* 23 (2013): 44-50.

7. Horinouchi T1., *et al*. "Endothelin-1 suppresses insulin-stimulated Akt phosphorylation and glucose uptake via GPCR kinase 2 in skeletal muscle cells". *British Journal of Pharmacology* 173.6 (2016): 1018-1032.

8. D'Antoni S., *et al*. "Endothelin-1 Induces Degeneration of Cultured Motor Neurons Through a Mechanism Mediated by Nitric Oxide and PI3K/Akt Pathway". *Neurotoxicity Research* 32.1 (2017): 58-70.

9. Hotta K., *et al*. "Daily muscle stretching enhances blood flow, endothelial function, capillarity, vascular volume and connectivity in aged skeletal muscle". *The Journal of Physiology* 596.10 (2018): 1903-1917.

10. Spier SA., *et al*. "Effects of ageing and exercise training on endothelium-dependent vasodilatation and structure of rat skeletal muscle arterioles". *The Journal of Physiology* 556 (2004): 947-958.

11. Angus Richard J A., *et al*. "Distortion of KB estimates of endothelin-1 ETA and ETB receptor antagonists in pulmonary arteries: Possible role of an endothelin-1 clearance mechanism". *Pharmacology Research and Perspectives* 5.6 (2017): e00374.

12. Matthew J Delmonico and Darren T Beck. "The Current Understanding of Sarcopenia Emerging Tools and Interventional Possibilities". *American Journal of Lifestyle Medicine* 11.2 (2017): 167-181.

13. Rosenberg I. "Epidemiologic and methodologic problems in determining nutritional status of older persons-Proceedings of a meeting held in Albuquerque, New Mexico, October 19-21, 1988". *The American Journal of Clinical Nutrition* 50 (1989): 1231-1233.

14. Alfonso J Cruz-Jentoft., *et al*. "Sarcopenia: revised European consensus on definition and diagnosis". *Age Ageing* 48.1 (2019): 16-31.

15. Orlando Angulo. "Sarcopenia prevalence in 40 years old and older patients in a cardiac rehabilitation centre". Clinical and biochemical criteria at the hospital infantil de San Jose, Bogotá -Colombia. Graduation Thesis.

16. Lemarié CA., *et al*. "Mthfr deficiency induces endothelial progenitor cell senescence via uncoupling of eNOS and downregulation of SIRT1". *American Journal of Physiology-Heart and Circulatory Physiology* 300.3 (2013): H745-753.

17. Marchesi C., *et al*. "Endothelial nitric oxide synthase uncoupling and perivascular adipose oxidative stress and inflammation contribute to vascular dysfunction in a rodent model of metabolic syndrome". *Hypertension* 54.6 (2009): 1384-1392.

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