

A review of epigenetic nutrients on chronic inflammation associated with sarcopenic obesity in the elderly†

노인의 저근육형 비만에 따른 만성염증 억제를 위한 후생유전학적 영양에 관한 고찰

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초 록

노인에게서 두드러지게 나타나고 있는 저근육형 비만은 근육감소를 동반한 체지방의 증가로 신체상의 뚜렷한 체성분의 변화를 야기시킨다. 이때 골감소증을 동반하여 신체기능의 감소 및 골절장애 그리고 대사성 관련 질환의 위험도가 올라가는 것으로 보고되고 있다. 노화로 인한 체성분의 변화는 단순한 저근육형일 경우와 비만일 때 보다 급격히 증가된 복부내장 지방조직에서 분비되는 염증성 사이토카인, C-반응성 단백질(CRP), 인터루킨(IL)-6, IL-8 및 종양 괴사 인자(TNF- α)들이 단백질 대사를 저해하여 근육량의 감소를 더욱 촉진시키며, 염증관련 대사질환의 유병률에 중요한 요인이다.

본 연구에서는 DNA 메틸화가 당뇨병, 심혈관질환, 암과 같은 만성염증성 질환에 관계하고 있다는 최근 연구 결과를 기초로 하여 항염증 영양소와 생리활성을 갖는 식품인자들의 충분한 섭취가 염증조절에 중요하게 기여할 것으로 생각되며, 또한 염증성 질환의 주요 표식자인 DNA 메틸화와 히스톤 변형을 유발하는 효소의 활성 또는 비 암호화된 RNA의 발현을 조절함으로써 근육량 증가와 체지방 감소에 중요한 역할을 하는 것을 살펴보았다.

따라서 최근 새롭게 인식되는 후생유전학적 연구의 중심에 있는 항염증 영양소의 효과와 체성분 변화와의 긍정적 관계를 중심으로 저근육형 비만의 예방 및 인구고령화에 건강한 노화를 위한 효과적인 방법을 제시하였다.

주제어: 저근육형 비만, 체성분 변화, 염증, DNA 메틸화, 항염증 영양소

I. Introduction

Modern society faces new challenges directly linked to our way of life, namely stress, obesity, and aging population. Among those, aging population linked with

obesity could significantly deteriorate the quality of life (Baumgartner, 2000). Aging is characterized by increased abdominal adiposity and decreased skeletal muscle mass and strength. Recently, it has been diagnosed as sarcopenic obesity (SO), when even it

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occurs in individuals with stable body weight (Lim *et al.*, 2010). It is thought to be caused by complex interactions between sedentary lifestyles, dietary changes, and hormone changes. This body composition changes in SO could impair the anabolic response of muscles. This could directly and indirectly lead more catastrophic influence including stimulating protein breakdown and suppressing muscle synthesis and increase several chronic inflammatory diseases and cancer risk (Wannamethe *et al.*, 2007).

The proportion of SO in the U.S. population aged 65 and over was predicted to rise from 12.4% in 2004 to 20% in 2030 (He *et al.*, 2005). Similarly, the Korean population is rapidly aging and Korea is becoming an aged society like other countries. Approximately 20.3% of the Korean population will be aged 65 and older in 2027 and 34.4% in 2050 (Chung *et al.*, 2013). However, SO in the elderly is often underestimated. Moreover, more studies should be needed on SO-induced chronic diseases and also on the prevention of SO.

In this review, we focus on the relationship between body composition in SO and chronic inflammation risk. Further, we try to show the effect of nutrition on the prevention of SO in the elderly. Recently, there emerge data of certain effects of modifying the diet composition such as anti-inflammatory nutrients and micronutrients and regular physical exercise to improve healthy aging by reversing disease-prone epimutations such as abnormalities in DNA methylation, histone modifications, chromatin remodelling, and microRNA (miR) patterns which are important hallmarks of inflammatory disease states (Barnett *et al.*, 2010; Szcic *et al.*, 2010). In this respect, "Let food be your epigenetic medicine" could represent a novel interpretation of what Hippocrates said already 25 centuries ago (Robertson, 2005). As such, it will be a challenge for future anti-inflammatory therapeutics and preventive SO research to identify novel epigenetic targets which allow selective modulation of the inflammatory signaling network in the diseased tissue and/or micro-environment (Deorukhkar *et al.*, 2007).

This review aims to summarize environmental factors, mainly nutrition and exercise helpful for reducing the risks of SO in the elderly. This will be envisaged to provide effective ways to prevent SO and the related prevalent chronic diseases as well. In this review, we discuss the possible epigenetic contributions of anti-inflammatory nutrients including fruits, vegetables, spices, vitamin D, EPA, and good quality of protein like leucine in chronic inflammation associated with SO in the elderly.

II. What is SO?

SO has been recently defined as an age-associated phenomenon with both a progressive increase in fat mass, even its distribution, and changes and decrease in muscle mass that occur in relatively weight-stable healthy individuals. SO in the elderly is associated with a loss of independence and metabolic complications and represents a major public health challenge in individuals over the age of 65 years (Kim *et al.*, 2009). Age-related changes in body composition may lead to increased secretion of a number of pro-inflammatory cytokines such as TNF- α , IL-1, IL-6, IL-12 or IL-23, major histocompatibility complex (MHC) molecules, and nitric oxide synthase secreted by the accumulation of abdominal fat. A reduction in muscle mass and physical activity reduces total energy expenditure in the elderly and may lead to weight gain (Schaap *et al.*, 2006). In this process, insulin resistance, energy metabolism, and growth hormone secretion occur to lead to leptin resistance and to a reduction of fatty acid oxidation in muscles, contributing to ectopic fat deposition in organs such as the liver, heart, and muscles and, in turn, to the loss of muscle quality in obese elder (Cororan *et al.*, 2007; Rasmussen *et al.*, 2006).

The amount of triglycerides in muscle increases with aging has been observed in a 2-year follow-up study of American healthy elderly. Muscle fat infiltration has

also been observed in some forms of muscular dystrophy and in disuse atrophy. Age-related infiltration of muscle fat warrants attention as it has been shown to be associated with reduced strength, incidence of mobility disability, and insulin resistance (Delmonico *et al.*, 2009). The fact that fat infiltrated muscle is more prone to inflammation than muscle without fat infiltration, suggests a connection between fat mass gain, muscle triglycerides content, and inflammation.

Such a vicious circle may lead to more SO and then to further weight gain, less muscle strength, and inflammation. Both aging and obesity are associated with a progressive deterioration of muscle quality. To understand the connection between fat mass gain and inflammation, aging and sarcopenia seem to be crucial and deserve particular attention. Therefore, more concerns are needed for keeping important factors such as muscle quality and the infiltration of fat into muscle for preventing SO.

III. The relationship between inflammation and body composition in SO

There are complex relationships between inflammation and SO in the elderly. In the aging process, fat-mass gain and muscle-mass loss together lead to elevated adipose tissue infiltration in skeletal muscle (Stenholm *et al.*, 2008), which accelerates disability, insulin resistance, inflammatory cytokine production, dyslipidemia, coagulation, lymphocyte activation, atherosclerosis, and osteoporosis, and stimulates breakdown of skeletal muscle (Hilton *et al.*, 2008). Those state can be recovered by calorie restriction and regular exercise (Kim *et al.*, 2010). Furthermore, in the case of diabetes melitus, breakdown of skeletal muscle by improper insulin secretion and reduced physical functioning has also been shown. Also, excess cytokine production from adipose tissue cells has been shown to impact sarcopenia by promoting the deterioration of skeletal muscle fiber

(Zoico *et al.*, 2010).

When the energy storage load of adipocytes becomes overwhelming of the function, adipocyte stress leads to the elevation of the level of C-reactive protein (CRP), interleukin (IL)-6, IL-8, and tumor necrosis factor (TNF)- α that affect a low grade inflammation (Cave *et al.*, 2008). In the end, its most probable outcome is insulin resistance and inflammatory disease (Cave *et al.*, 2008). Elevated production of proinflammatory adipokines from adipocytes recruit immune cells and then attribute to adipose tissue macrophage (ATM) function. ATMs secrete monocyte chemotactic protein-1 (MCP-1) which recruits monocytes producing TNF- α in liver, fat, and muscle and promotes insulin resistance (Clària *et al.*, 2011).

Also, lipotoxicity dietary nutrients (arachidonic acid (AA) and saturated fats) cause proinflammatory eicosanoids (leukotrienes) that can disrupt hormonal signaling pathway between hormone receptors and their internal targets giving rise to insulin and leptin resistance (Hubbard *et al.*, 2008). It has also been shown that AA has a direct effect on the activation of nuclear factor-kappa B (NF- κ B). NF- κ B is a key proinflammatory gene modulator in potentially transforming inflammation into chronic disease. Environmental factor, physical inactivity, malnutrition, and hormonal change may more contribute to chronic inflammation and oxidative stress through activation of transcription factors such as NF- κ B (Sears *et al.*, 2011; Kennedy *et al.*, 2009).

The current study demonstrates that insulin resistance induced low-level inflammation is an important factor in the change of body composition in aging and physical dysfunction and that it could mediate chronic disease.

IV. Epigenetic nutrients on SO

Recently, there are big interests focusing on modulating gene expression against SO which is related to complex inflammation status. Many studies show the

effects of SO management based on the beneficial role of nutritional factors. SO is accelerated by decreased physical activity, testosterone, and growth hormone deficiency (Malafarina *et al.*, 2012). However, mild cytokine excess, inflammation, and the stress response in SO status can be reversibly changed by regulating DNA methylation. DNA methylation that may alter gene expression but do not involve changes in the DNA sequence is the best-known epigenetic marker. DNA methylation has been well known to be linked to several chronic inflammatory diseases such as cancer, diabetes, heart disease, and neurological disorders. Modulating DNA methylation of inflammatory genes by using dietary factors and exercise is an effective approach to cure SO and inflammatory disease as well (Robertson & Wolffe, 2000; Poirier, 2002). Inadequate DNA methylation caused from dietary methyl insufficiency can alter immune function and major inflammatory genes factors in chronic inflammatory and metabolic disorders. Also, oxidative stress and inflammatory damage play an important role in epigenetic reprogramming of expression of cytokines (Geisler *et al.*, 2004). Therefore, SO therapeutic strategies are based on nutritions that can modulate inflammatory gene expression affecting epigenetic mechanisms by anti-inflammatory nutrients and regulate sarcopenia by adequate protein and vitamin D intake.

In the methylation cycle, methionine is converted to SAM (S-adenosylmethionine) which is the primary source of methyl groups for most other biochemical reactions including methylation of DNA, RNA, protein, neurotransmitter, and creatinine. At the same time, it becomes SAH (S-adenosylhomocysteine) which is metabolized to homocysteine as competing with SAM for binding on DNA methyltransferase (DNMT) correlate with DNA hypomethylation (Yideng *et al.*, 2007). As a result, elevation of blood homocysteine concentration is a key in vascular diseases and DNA methylation can be regulated by SAM:SAH ratio in the methylation cycle. Therefore, deficiencies in either folate or vitamin B₁₂ dietary intakes should be considered about reducing the SAM:SAH ratio and

influencing DNA methylation (Lund & Zaina, 2009; Jones & Liang, 2009).

Adequate level of homocysteine derives from methionine (protein from animal sources like meat, egg, and milk), vitamin B₂, B₆, B₁₂, and folic acid in the body is broken down into harmless waste products or protein building blocks (Niculescu & Zeisel, 2002). These nutrients are integrally involved in 1-carbon metabolism. Even transient exposure to polyphenolic phytochemicals interfere with enzymatic activity of DNMT, Class I, II, IV Histone deacetylases (HDAC), histone acetyltransferase (HAT) and Class III HDAC, sirtuins (SIRT) of key inflammatory genes could modulate immune homeostasis (Rahmana *et al.*, 2006). As such, adequate DNA methylation through nutritional epigenetic effect will be a challenge for SO.

1. Protein intake

As aging commonly proceeds along with the unbalance of fat to muscle ratio and bone mineral density as well, the consequence is altering energy balance of the elderly which is exacerbated by oxidation stress process. Alteration of energy balance by body composition related oxidative stress exacerbates the loss of muscle mass (Paddon-Jones & Rasmussen, 2009). Adequate and good quality of protein intake is important for maintaining muscle mass in the elderly with SO. Many studies reported that supplying enough the branched-chain amino acid, leucine could initiate protein synthesis and 20 - 30 grams of protein at every meal are recommended to maintain muscle (Layman, 2009).

2. Vitamin D

Recently, vitamin D deficiency is common in the elderly in worldwide and many studies have demonstrated a link between vitamin D level and sarcopenia. There are several mechanisms of vitamin D in muscle cell metabolism (Visser *et al.*, 2003). Vitamin D regulates calcium homeostasis, protects

skeletal muscle from insulin resistance, stimulates the proliferation and differentiation of myoblast, influences fatty degeneration in muscle, and induces the release of AA which may alter membrane fluidity and permeability. Therefore, 25 (OH) vitamin D levels should be measured in all the individuals with sarcopenic obesity and vitamin D supplementation should be recommended sufficiently to increase levels above 100 nmol/L in the elderly (Lips *et al.*, 2010; Dirks-Naylor & Lennon-Edwards, 2011).

3. Anti-inflammatory nutrients

The most obvious solution for preventing SO is to reduce epigenetic factors causing inflammation by anti-inflammatory nutrients. Anti-inflammatory nutrients as the main aspect of the environment inhibit toll-like receptors and TNF- α or activate anti-inflammatory gene transcription factors such as peroxisome proliferator-activated receptor alpha (PPAR α) and PPAR γ (Dubuquoy *et al.*, 2006). They enhance the capacity of the adipose tissue for resequestering accumulated fat in other tissues, thus reversing lipotoxicity by producing new healthy fat cells. These lipotoxicity dietary nutrients (AA and saturated fats) disrupt hormonal signaling patterns and give rise to insulin and leptin resistance (Kern, 2003). However, by either directly inhibiting the formation of AA or intaking high level of EPA can dilute out the concentration of AA in the cell membrane and pro-inflammatory eicosanoids such as leukotrienes (Payan *et al.*, 1986).

A couple of suggestions have been reported as being effective in reducing inflammation. Firstly, low intake of both omega-6 and saturated fats, which is thought to interact with the innate immune system (Kiecolt-Glaser *et al.*, 2007). Secondly, as with EPA, low glycemic load diets and polyphenols, which help not only to inhibit NF- κ B, but also activate activated protein (AMP) kinase (Zang *et al.*, 2006). Anti-inflammatory nutrient consumption and physical exercise increase lean body mass to reduce effectively age-related SO risk.

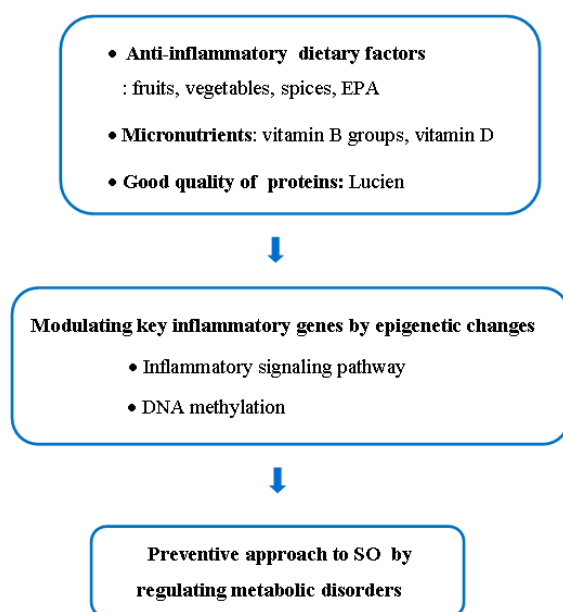
V. Conclusion

Age-related muscle loss and fat increase cause low level inflammation affecting the prevalence of chronic diseases in the elderly. In facing an era of rapid aging, recognition of SO is important in a significant risk factor for the elderly health.

What reduces epigenetic factors causing inflammation?

Genes are not an absolute factor of our fate. Most biology will come from the complex interaction of all the proteins and cells working with environmental factors, not driven directly by the genetic code. An effective approach to the cure or protection against SO and inflammatory disease is to modulate key inflammatory genes by dietary factors and exercise. In figure 1, adequate nutrients and other good life styles show us the summary for the most effective epigenetic intervention to reverse SO in the elderly. Recently, several studies reported that a moderate weight loss (nearly 5%) in a group of elderly women determines a significant improvement in insulin resistance, fat distribution, and more importantly of muscle lipid infiltration. But moderate weight loss and anti-inflammatory nutrients including fruits, vegetables, spices, vitamin D, EPA, and good quality of protein like leucine may improve function and preserve muscle mass in the obese elderly. Further studies will be necessary to confirm these findings and to understand how diet contribute to the improvement of the body composition of SO. Also, looking more at the human genome for solutions to most chronic illnesses including the diagnosis, prevention, and treatment of SO cannot be overemphasized in today's world.

Keywords: Sarcopenic obesity, body composition change, inflammation, DNA methylation, anti-inflammatory nutrients



[Figure. 1] The effective epigenetic nutrients to reverse SO

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