Chronic Low-grade Inflammatory Phenotype (CLIP) and Senescent Immune Dysregulation

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ABSTRACT

Purpose: The aim was to provide an overview of chronic low-grade inflammatory phenotype (CLIP) and evidence for its role in the pathogenesis of frailty and other chronic conditions as well as potential causative factors and interventions.

Methods: We reviewed evidence from published clinical and laboratory studies and summarized the opinions of experts from published reviews.

Findings: CLIP is a low-grade, systemic, unresolved, and smoldering chronic inflammatory state clearly indicated by a 2- to 4-fold increase in serum levels of inflammatory mediators, such as interleukin-6 and C-reactive protein. It involves many other cellular and molecular inflammatory mediators. CLIP typically occurs during aging, also known as "inflammaging," and is an integral part of the spectrum of immunosenescence. Causative factors likely include persistent viral infections, particularly chronic cytomegalovirus infection, cellular senescence, failure to eliminate degraded materials and waste products, dysregulated microbiota and gut permeability, obesity, and others. Substantial evidence supports CLIP as a powerful contributing factor to frailty and many other chronic conditions and adverse health outcomes. Many of the inflammatory mediators and their regulatory mechanisms in CLIP may serve as potential targets for therapeutic intervention. However, development of new interventional strategies for CLIP and its associated chronic conditions should take the complexity of the inflammatory network into consideration. Nonpharmacologic interventions, such as caloric restriction and exercise, may have significant impact on CLIP and its causative factors, leading to substantial health benefits. Metformin and resveratrol have anti-inflammatory property and may serve as a promising therapeutic agent for treatment of CLIP and frailty.

Implications: CLIP is a chronic inflammatory pathophysiologic process that plays an important role in the pathogenesis of frailty and many other chronic conditions. Improving our understanding of this phenotype may provide opportunities to identify potential targets of effective prevention and therapeutic strategies for frailty and other CLIP-associated conditions. (*Clin Ther*. 2019;41:400–409)

Keywords: CLIP, inflammaging, frailty, immune senescent remodeling, cytomegalovirus, aging.

INTRODUCTION

Traditionally, inflammation is regarded as an immediate protective response to insults such as infections and traumatic injuries. Inflammation, either acute or chronic, is a protective response that kills, inactivates, or walls off the injurious agent. At the same time, it may also trigger a cascade of events that heal and reconstitute damaged tissue, either by regeneration of native parenchymal cells, filling the defect with fibroblastic tissue (fibrosis or scarring), or both processes. A physiologic inflammatory response, like many other immune responses, is highly regulated with prompt initiation and timely resolution.[1,2] This is because too little or too late of this response would not provide effective protection. However, an uncontrolled or unresolved inflammatory response would potentially be harmful and lead to many acute and chronic diseases.

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Chronic low-grade inflammatory phenotype (CLIP), originally coined by Krabbe et al[3] in 2004, is an alternative and more indolent systemic inflammatory state. Its clinical and biological importance has increasingly been recognized over the past decade. CLIP differs from the classic inflammation in its chronicity and magnitude. It is typically, but not exclusively, associated with aging, likely resulted from accumulative effects of inflammatory responses to numerous and/or persistent antigenic stimuli as well as senescent immune dysregulation. In contrast to traditionally defined inflammatory responses, CLIP represents a chronic inflammatory trait that lacks localization or apparent antigenic stimulus. This article provides a brief overview of CLIP, focusing on its definition, clinical significance particularly its role in contributing to frailty, causative factors, and mechanisms, including its relationship with senescent immune dysregulation, as well as intervention.

DEFINITION

CLIP is a low-grade, systemic, unresolved, and smoldering chronic inflammation clearly indicated by a 2- to 4-fold increase in serum levels of inflammatory mediators, including interleukin-6 (IL-6) and acute phase proteins, for example, C-reactive protein (CRP). However, there is no numerical cut off values for elevated inflammatory mediators to define CLIP at the present time. Figure 1 illustrates CLIP characterized by elevated blood levels of IL-6 and CRP in the absence of evident immediate triggers.[4] In addition to IL-6 and CRP, a large number of cellular and molecular inflammatory components are involved in CLIP or are produced as a result of inflammatory processes that lead to CLIP.[5–7] For example, moderately elevated counts of total leukocytes, granulocytes, and activated monocytes have been well documented in CLIP or inflammaging. A wide range of pro- and anti-inflammatory mediators have also been described in the literature, including (1) cytokines and their soluble receptors or associated molecules, such as IL-1, IL-1 receptor antagonist, IL-6, IL-8, IL-13, IL-18, interferon-α and interferon-β, tumor necrosis factor (TNF) and its soluble receptors 1 (sTNFR-1) and 2 (sTNFR-2); (2) CC chemokine ligands 2, 3, and 5; (3) adhesion molecules, such as vascular cell adhesion molecule 1, intercellular adhesion molecule 1, and E-

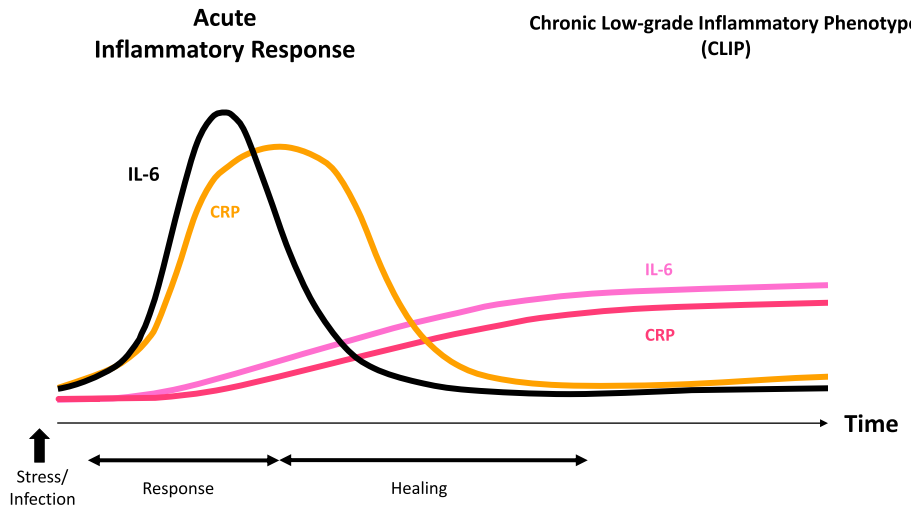

Figure 1. Acute inflammatory reaction versus chronic low-grade inflammatory phenotype (CLIP). Acute inflammatory reaction (left) as a response to a stress or an infection with rapid rise in circulating levels of interleukin (IL)-6 and C-reactive protein (CRP). Such levels gradually fall back to the baseline as the response is resolving (healing). CLIP (right) as indicated by sustained elevation of circulating IL-6 and CRP levels, albeit not up to the peak levels achieved during the acute response, indicates CLIP as a low-grade, systemic, unresolved, and smoldering inflammatory trait. Adapted with permission.[4]

selectin; and (4) acute-phase reactants, such as CRP, serum amyloid A, and fibrinogen. This list continues to grow rapidly.

As such, CLIP is a chronic inflammatory trait with significant clinical and biological implications in senescent immune dysregulation, vulnerability to acute infections, and development of frailty and many other chronic conditions. CLIP typically occurs during aging, also known as "inflammaging," a term initially described by Claudio Franceschi.[5] Although CLIP and inflammaging can be used interchangeably in the context of aging, CLIP is not exclusively associated with aging. McDade[8] has described that early environments and childhood antigenic exposures may significantly affect one's immunity and development of CLIP.[8] CLIP also differs from autoimmunity despite that the same inflammatory mediators may be involved in both. In autoimmunity, autoantibodies can often be identified and levels of pro-inflammatory mediators tend to be much higher than those observed in CLIP, resulting in specific autoimmune diseases, such as rheumatoid arthritis.[9]

CLINICAL SIGNIFICANCE

Studies suggest that CLIP is a powerful risk factor for frailty and a number of other pathophysiologic processes, chronic conditions, and adverse health outcomes, including atherosclerosis and cardiovascular diseases (CVDs), neurodegeneration and Alzheimer's disease, insulin resistance and type 2 diabetes mellitus, tumorigenesis and cancer, osteoporosis, anemia, chronic kidney disease, depression, sarcopenia, and disability (Figure 2).[4–6] One unique feature of CLIP is that it serves as an important risk or pathophysiologic factor for these seemingly unrelated chronic conditions. The clinical significance is that these chronic diseases are highly prevalent and frequently lead to frailty, disability, and early mortality.

A large and growing body of evidence, including that from us, has provided supportive evidence for a role of CLIP in contributing to frailty. This has substantial clinical implications because frailty is a common and important clinical syndrome in older adults characterized by depleted physiologic and functional reserve, involving multi-organ systems and increased vulnerability to serious adverse health outcomes, including falls, hospitalization, disability, dependence, and early mortality. These studies

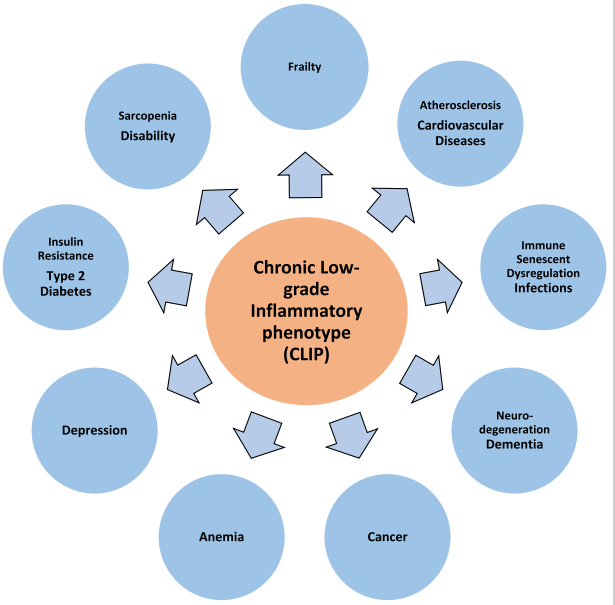

Figure 2. Central role of chronic low-grade inflammatory phenotype (CLIP) in contributing to frailty, major pathophysiologic processes, and chronic diseases.

typically use the phenotypic definition of frailty, according to which frailty is defined as a distinct clinical syndrome that meets ≥3 of the 5 phenotypic criteria: weakness, slowness, low level of physical activity, self-reported exhaustion, and unintentional weight loss.[10] Although in-depth review of this active area of research is beyond the scope of this overview, several lines of scientific evidence are emphasized here, highlighting the role of CLIP in contributing to frailty. First are molecular mediators of CLIP and immune activation. Direct association between frailty and increased IL-6 levels was first observed in community-dwelling older adults.[11] Subsequent studies have shown such associations with other CLIP mediators, including CRP and other molecular mediators.[12,13] In addition, elevated levels of neopterin, a well-established marker for immune activation, are associated with frailty,[14] suggesting the involvement of immune activation upstream of CLIP in the pathogenesis of frailty. Second are the cellular components of CLIP. Drastic increase (above the population-defined normal range) of leukocyte

count, the cellular component of inflammation routinely measured in clinical practice, is recognized as a laboratory indicator for acute systemic inflammatory responses most commonly to acute bacterial infections. Studies have reported direct associations between frailty and increased leukocyte count, albeit still under the upper limit of the normal range, and counts of its specific subpopulations, including neutrophils and monocytes.[15,16] In T-lymphocyte subpopulation, frailty is associated with increased counts of $CD8^+CD28^-$ T cells and $CCR5^+$ T cells, the latter of which has a type-1 pro-inflammatory phenotype.[17–19] Last is the impact of CLIP on other physiologic systems. Because frailty involves multisystem physiologic dysregulation, it is conceivable that CLIP contributes to frailty through its detrimental impact on other physiologic organ systems, such as musculoskeletal and endocrine systems, anemia, clinical and subclinical CVDs, and nutritional dysregulation.[7,20–22] In fact, studies have shown that elevated cellular and molecular inflammatory mediators have inverse associations with hemoglobin concentrations, insulin-like growth factor 1 levels, and levels of albumin, micronutrients, and vitamins.[15,23–26] Taken together, it has been proposed that CLIP plays a key role in the pathogenesis of frailty, directly or indirectly through other intermediate pathophysiologic processes.[27]

Although CLIP is known for its strong associations with many other chronic conditions, mechanisms that underlie these associations are far from being elucidated. For example, it is unclear whether CLIP causally contributes to these conditions or whether CLIP is a reactive marker of another underlying pathologic process. However, these 2 mechanisms are not mutually exclusive. For example, atherosclerosis is considered to be secondary to accumulation of cholesterol-containing, oxidized LDL particles in the arterial wall after endothelium damage, which seems unrelated to CLIP. However, oxidized LDL particles trigger an inflammatory response that can persist without timely resolution.[28] Activation of innate and adaptive immunity and subsequent CLIP actively contribute to the initiation and progression of atherosclerosis, from early or further endothelial dysfunction and damage, acute thrombotic complications triggered by plaque rupture, to arterial wall fibrosis, calcification, stiffness and stenosis, leading to the development of acute and chronic CVD. Therefore, CLIP contributes to the initiation and/or acceleration of this vicious cascade of events in the pathogenesis of atherosclerosis and CVD. Clinically, CLIP is considered not only as a CVD risk factor but also a predictor for disease progression, and serum CRP level is now routinely monitored in patient care practice.[29]

CAUSATIVE FACTORS AND MECHANISMS

As described in the section above, CLIP and its adverse health effects are well documented. However, causative factors and underlying mechanisms of CLIP have only just begun to be elucidated. Increasing research effort has been devoted to several key areas discussed in the paragraphs below.

First, persistent viral infections, such as those by cytomegalovirus (CMV) and HIV are likely an important causative factor. For example, chronic CMV infection is highly prevalent in the general geriatric population and aging HIV-infected (HIV^+) individuals. Human CMV is known to cause latent infection with subsequent reactivations. A unique feature of this virus is that it causes clonal expansion of T cells, leading to a large proportion, often >10% and can be 30% to 40%, of circulating T cells targeted to its vast antigenic epitopes.[30,31] In the Multicenter AIDS Cohort Study, our work has shown that CMV induces broad $CD4^+$ and $CD8^+$ T-cell responses, and such CMV-specific T-cell responses are directly linked to CLIP and frailty.[32,33] Some studies have observed direct associations of positive anti-CMV immunoglobulin G (IgG) serology with frailty and functional disability in older adults.[34,35] However, controversy exists because other studies have failed to identify such associations.[36,37] One possible explanation is that anti-CMV IgG serology is a crude measure that merely indicates prior exposure to the virus. It does not distinguish between past and chronic (persistent) infections. Our studies indicate that detection of CMV DNA in peripheral blood monocytes, rather than positive CMV serology, had strong associations between chronic CMV infection and increased frequencies of CMV pp65 (NLV)-specific $CD8^+$ T cells and also immune activation (elevated serum neopterin levels) in older adults.[38,39] Moreover, we have found higher serum IL-6 levels and increased CMV pp65 (NLV)-specific $CD8^+$ T cells in older women with chronic CMV infection as assessed by

CMV DNA in monocytes, again not by positive anti-CMV IgG serology.[40] Taken together, these findings support the hypothesis that chronic CMV infection is a potential important causative factor for CLIP, leading to its adverse health impact.

Second, cellular senescence and failure to eliminate degraded materials can be important sources of CLIP. Senescent cells can survive and accumulate in the circulation and in the tissues throughout the body. These senescent cells, although no longer able to proliferate or perform much of the designated physiologic function, acquire a senescence-associated secretary phenotype that involves secretion of a wide range of pro-inflammatory mediators, contributing to CLIP.[41,42]

It is well recognized that massic generation of large amount of damaged or worn-out molecules and organelles, cell debris, and waste products occurs constantly throughout life. At the same time, complex and well-regulated cellular and molecular machineries have evolved to constantly survey and eliminate these harmful biological materials, mainly through the mechanism of autophagy. However, the imbalance between the production and clearance processes results in their accumulation over time, leading to CLIP. For example, damage-associated molecular pattern molecules released from damaged or dying cells can accumulate and likely contribute to CLIP if not promptly removed.[43,44] These damage-associated molecular pattern molecules include reactive oxygen species from damaged and unrecycled mitochondria, extracellular nucleotides such as adenosine triphosphate, oxidized cardiolipin, free nuclear and mitochondrial DNA fragments or histones, high-mobility group protein B1, oxidized LDL, amyloid-β, islet amyloid polypeptide, and particulates such as monosodium urate and cholesterol crystals.

Third, dysregulated microbiota and gut permeability or gut dysbiosis can be another important source of CLIP. This relatively new hypothesis postulates that bacteria rather than the beneficial commensal microorganisms, also termed pathobionts, proliferate and take over healthy normal flora in the gut.[45] When coupled with increased mucosal barrier permeability, these bacteria and their products are able to translocate into the circulation. Bacterial products, such as pathogen-associated molecular pattern and microbial-associated molecular pattern molecules are potent stimuli to innate immunity once they are into the circulation and tissues, leading to CLIP. This hypothesis is supported by studies in animal models. However, no definitive evidence is available to prove causal relationship between gut dysbiosis and CLIP in humans with no overt inflammatory disease.[46]

Finally, obesity, particularly central or visceral obesity, is strongly associated with CLIP.[47] Adipocytes in visceral fat can produce adipokines and pro-inflammatory mediators, leading to CLIP. Weight loss through dietary reduction and possibly bariatric surgery is associated with improvement of CLIP. This is likely due to, at least in part, normalized expression of inflammatory genes in white adipose tissue and downregulation of the NLRP3 inflammasome.[48–50] Moreover, the visceral fat tissue of people who are obese is infiltrated by immune cells such as T lymphocytes and macrophages. These immune cells in the adipose tissue, when stimulated by adipokines, can serve as a powerful source of pro-inflammatory mediators. This is particularly true in the immune senescent or dysregulated environment, which is discussed next.

RELATIONSHIP WITH SENESCENT IMMUNE DYSREGULATION

Senescent immune dysregulation, or immunosenescence, is an essential underlying mechanism for CLIP or inflammaging. This is because both the innate and adaptive immunity, particularly leukocytes (neutrophils, lymphocytes, monocytes), macrophages, and cytokines, which are the major cellular and molecular components of the inflammation system, play an indispensable role in sensing, initiating, and mediating inflammatory responses. They also serve as key regulators of inflammation and its resolution. In fact, CLIP or inflammaging is considered as an integral part of the spectrum of immunosenescence.[5,35]

As discussed earlier, a physiologic inflammatory response, like many other immune responses, is highly regulated and tightly controlled, both in the initiation and magnitude of the response as well as in its resolution. One may consider that dysregulation in regulatory T cells (Tregs) may lead to the development of CLIP because Tregs are major T cells that regulate immune and inflammatory responses. However, Tregs are a heterogeneous T-cell population. Naturally occurring Tregs derived from

the thymus a $CD4^+CD25^+Foxp3^+$ phenotype, and inducible Tregs with the same phenotype can be induced from $CD4^+CD25^-Foxp3^-$ conventional T cells with transforming growth factor-β.[51] Emerging data suggest that during immunosenescence, although inducible Tregs tend to decrease, naturally occurring Tregs actually accumulate,[52] likely a compensatory phenomenon to counteract CLIP or inflammaging. In the geriatric syndrome of frailty, we conducted in-depth analyses of monocyte-mediated pathway-specific gene expression and found significant upregulation in *ex vivo* expression of a number of stress-responsive inflammatory pathway genes.[53] Moreover, this upregulation in monocytic expression of CXCL10, a potent pro-inflammatory chemokine, is highly correlated with elevation in circulating IL-6 levels,[53] suggesting inflammation pathway activation as an important part of the immune senescent dysregulation that leads to CLIP. However, mechanisms of such dysregulation resulting in inflammation pathway activation are likely complex and yet to be determined. To this end, it is believed that immune senescent dysregulation may serve as a prerequisite for CLIP causative factors described in the section above.

INTERVENTION

In a recently published review, Ferrucci and Fabbri[6] have listed randomized, controlled trials that tested the efficacy of new anti-inflammatory agents in preventing or controlling CVD clinical manifestations. For example, a clinical trial of canakinumab, a monoclonal antibody targeting IL-1β in patients with previous myocardial infarction and high CRP level, indicated its efficacy in preventing recurrent cardiovascular event and reducing CRP levels.[54] Despite this success, one should bear in mind a number of questions when considering new interventional strategies to prevent, mitigate, or treat CLIP and its associated frailty and other chronic conditions. For example, almost all the cellular and molecular pro-inflammatory mediators of CLIP are nonspecific, and their elevation is highly context dependent. Therefore, it is difficult to select any individual mediator or set of mediators as useful surrogate measures of clinical end points in any given interventional study.

Similarly, because CLIP typically manifests itself with increased levels of multiple pro-inflammatory mediators, it is difficult to determine which mediator, or a set of mediators, to target for intervention. The *in vivo* relationships and interactions among these multiple mediators in CLIP are likely complex and poorly understood. We conducted an analysis to evaluate the relationships between serum levels of IL-6 and sTNFR-1 and sTNFR-2 in the AIDS Linked to the Intra Venous Experience study, a large prospective cohort study of injection drug users, and found significant associations of IL-6 with sTNFR-1 and sTNFR-2.[55] This finding has led to the notion that TNF-α may serve as a key mediator that triggers or regulates the inflammatory pathway in CLIP with therapeutic implications. This is because TNF-α is a central player in the inflammatory cascade leading to systemic inflammation. By successfully targeting this upstream mediator, monoclonal antibodies against TNF-α have now become an indispensable armamentarium to treat rheumatoid arthritis.[9,56] In another analysis, when serum neopterin and CRP levels were added to the analysis described above,[55] we observed that neopterin was differentially associated with sTNFR-1 and sTNFR-2 rather than IL-6 or CRP.[57] These findings indicate that neopterin, being a mediator of immune activation, is associated with more proximal inflammatory mediators (sTNFR-1 and sTNFR-2) instead of distal mediators (IL-6 and CRP), suggesting a potential interventional target upstream of CRP and IL-6 that deserves further investigation. This therapeutic implication has been found in the field of CVD because serum CRP measurement is now incorporated in routine clinical assessment of chronic inflammation and atherosclerosis, and studies have started to move upstream to identify new targets for vascular protection.[58]

In addition to targeting the common inflammatory cascade, one should consider, if possible, removal or treatment of causative factors of CLIP, including those discussed in Causative Factors and Mechanisms. These causative factors are likely further upstream of immune activation and subsequent CLIP. However, the 2 strategies are not mutually exclusive. For example, sirtuin pathway modulators, such as resveratrol and sirtinol, are known for their anti-inflammatory property. For example, Timmers et al[59] observed that resveratrol supplement reduced TNF-α levels and leukocyte counts. Meanwhile, we have reported their anti-CMV

effects.[60] As such, these compounds can potentially be beneficial for both treating chronic CMV infection, that is, removal of one causative factor, and suppressing inflammatory cascade. Another compound, perhaps more promising, is metformin. Metformin is a first-line therapy for type 2 diabetes mellitus. Studies have shown its effect in reducing inflammatory markers[61] and its beneficial impact on obesity.[62]

Caloric restriction (CR) and exercise are arguably 2 of the most well-established nonpharmacologic interventions for multiple pathophysiologic processes, including CLIP. CR, in the absence of malnutrition, is known to delay aging through multiple mechanisms,[63] including its anti-inflammatory properties. CR has been shown to attenuate the development of CLIP as marked by elevated TNF-α, IL-1β, IL-6, and CRP levels.[64] Exercise training is well known for its health benefits. The impact of physical activity on inflammation varies, depending on the frequency, intensity, volume of exercise, and the individual's endurance capacity. For example, strenuous exercise may increase local and systemic production of pro-inflammatory cytokines, likely resulting from muscle damage and subsequent inflammation. However, moderate and regular physical activity has been shown to reduce levels of TNF-α, IL-6, and CRP and, therefore, improves CLIP in healthy older adults. In addition, aerobic exercise in older men decreases serum IL-6 levels and increases IL-10 levels, a potent anti-inflammatory cytokine that downregulates CLIP.[65] Taken together, the health benefits of these nonpharmacologic modalities are due, at least in part, to their modulating effects on CLIP.

CONCLUSION

CLIP, a low-grade, systemic, and smoldering chronic inflammation as marked clearly by a 2- to 4-fold increase in levels of mediators that involves a large number of cellular and molecular inflammatory components has increasingly been recognized for its role in contributing to frailty and other age-related chronic conditions. CLIP is considered as an integral part of the spectrum of immunosenescence. Potential causative factors include chronic CMV infection, senescence-associated secretary phenotype, gut dysbiosis, and obesity. Although CR and exercise are major nonpharmacologic strategies to intervene CLIP and frailty, metformin and resveratrol have indicated a potent anti-inflammatory property. Improving our knowledge about CLIP and its complex network of inflammatory mediators will help develop effective prevention and treatment of CLIP, frailty, and other age-related chronic conditions in older adults.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinthera.2019.02.001.

CONFLICTS OF INTEREST

All authors declare no financial or any other conflict of interest. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

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