Can Blood Parameters Predict the Risk of Locomotive Syndrome in Middle-Aged and Older Individuals? A Literature Review

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ABSTRACT

Locomotive syndrome (LS) is related to shortcoming and loss of capacity in the musculoskeletal framework. In spite of the fact that there is only limited information on the incorporation between blood parameters and LS, recent proofs recommend that serum cystatin C, hemoglobin A1c, albumin, and dehydroepiandrosterone-sulfate levels are in relation with the risk of LS. These findings imply that these blood parameters are an attainable instrument for screening the in danger grown-up population for LS. This literature review aimed to summarize the current understanding of the relationship with LS and blood parameters in middle-aged and older people.

This would facilitate initial detection and therapy of the LS and minimize the negative effects of LS on the activities of daily life and develop that the quality in life functioning.

Keywords: Albumin; Cystatin C; Dehydroepiandrosterone-sulfate; Hemoglobin A1c; Locomotive syndrome; Blood parameter; Screening tools

Abbreviations: DHEA-S: Dehydroepiandrosterone-sulfate; GH: Growth Hormone; GLFS: Question Geriatric Locomotive Function Scale; HbA1c: Hemoglobin A1c; IGF-I: Insulin-like growth factor-I; JOA: Japanese Orthopedic Association; LS: Locomotive Syndrome; TNF-α : Tumor Necrosis Factor-α

INTRODUCTION

Any impairment in the locomotive tissues prompts pain, a limited range of motion at the joints or spine, muscle weakness, and balance deficits, thereby resulting in locomotive syndrome (LS). The term "LS" was proposed in 2007 by the Japanese Orthopedic Association (JOA) to describe individuals with locomotive organ impairment [1]. This syndrome is caused by weakness and impaired-function of musculoskeletal organs, including the bones, joints, and muscles. These functional deficits lead to difficulties in standing, walking, running, climbing stairs, and performing other physical functions essential for mobility in daily life [1]. In 2013, the JOA developed evaluation methods for estimating the risk factors of LS across a broad scope of age [2,3]. These consists 3 functional examinations: the stand-up test, the two-step test, and assessment with the 25-question geriatric locomotive function scale (GLFS). In 2018, 65 years old or more accounted for 28.1% of the Japanese populace. The nation faces the advent of a "super-aged" nation before and faster than any other nation worldwide. Estimates indicate that older individuals will account for 38.4% of the country's total population by 2065. Therefore, despite advances in LS screening methods, other predictive indicators for LS should be developed to detect and treat the syndrome earlier and to reduce the risk of LS in the general population. It has been well known that blood parameters are effective screening tools for identifying the risk for metabolic syndrome and other chronic diseases [4,5]. However, the potential relationship between blood parameters and LS is still to be established. We have recently demonstrated that higher hemoglobin A1c (HbA1c) and lower albumin levels were associated with a higher prevalence of LS among Japanese middle-aged and older individuals (age 40-85 years) [6]. We have also found that low dehydroepiandrosterone-sulfate (DHEA-S) levels might be a useful screening tool for LS in men [6]. In that study, we found no significant differences in the levels of several anabolic hormones, including growth hormone (GH), insulin-like growth factor (IGF)-I, and testosterone, between individuals with and without LS of both sexes [6]. Normal aging results in

decreased circulating levels of GH, IGF-I, testosterone, and DHEA-S. This decrease might contribute to the changes in muscle mass and function seen in older people [7], suggesting that the potential blood markers for LS might be different from those for sarcopenia.

Moreover, other investigators have reported that high levels of cystatin C is a potential predictor for the risk of LS in older people [8]. The cystatin C level is a muscle mass-independent measure of kidney function, unlike the creatinine level. Thus, it can be suggested that these blood parameters might be effective screening tools for predicting the risk of LS and other related diseases in a super-aged society. Nonetheless, the association between blood parameters and LS has not been established yet in either Japanese adults or in any other population worldwide and information on such associations is still limited. The purpose of this literature review was to summarize the current understanding of the association between LS and blood parameters in middle-aged and older individuals.

ASSOCIATION BETWEEN THE RISK OF LS AND BLOOD PARAMETERS

The following sections introduce and discuss the current understanding regarding potential blood parameters as predictors of the risk of LS in middle-aged and older individuals.

Cystatin C

Recent study has shown that the serum cystatin C level is related to the risk of LS and can be used as an early predictor in Japanese middle-aged and older community-dwelling people. Cystatin C, a cysteine protease inhibitor of the lysosomal protease enzyme, is used as a clinical predictor for renal function, cardiovascular disease, and diabetes-related mortality [8]. Cystatin C regulates protein catabolism, bone resorption, inflammation, hormone processing, antigen presentation, and the T-cell-dependent immune response. Although small amounts of catalytically active cystatin C are found under normal conditions, the serum cystatin C level is significantly higher in subjects aged ≥ 60 years with a risk of LS. A receiver operating characteristic curve analysis confirmed that serum cystatin C level is a good predictor of LS risk, with 79.3% sensitivity and 76.0% specificity. Note that higher cystatin C concentrations were linearly associated with inadequate exercise capacity and heart rate recovery in older adults [9]. Thus, when high serum cystatin C levels are detected, it is strongly recommended to perform the tests for LS risk.

Hemoglobin A1c

Recently we demonstrated that higher HbA1c levels are associated with the prevalence of LS in 223 Japanese middle-aged and older people [6]. We found that participants with an HbA1c level ≥ 5.7% had a higher risk for LS than those with an HbA1c level <5.7%, with an odds ratio of 2.62. HbA1c is widely used worldwide as one of the diagnostic criteria for diabetes since it reflects glucose metabolism and the overall metabolic control over the preceding 6-8 weeks [10]. Moreover, the American Diabetes Association and the World Health Organization have proposed the use of HbA1c levels to identify individuals at high risk of developing type 2 diabetes based on a cutoff value of 5.7% (range of 5.7%-6.4%) [11]. When evaluating the association of HbA1c with physical functions and body composition in LS participants, our data showed that HbA1c levels are negatively correlated with the maximal 10-m walking speed and positively correlated with the body mass index. Therefore, HbA1c levels seem to be higher in individuals who do not exercise regularly or who have low levels of physical activity. Furthermore, a meta-analysis demonstrated a reduction in HbA1c levels following an aerobic exercise program in diabetes patients [12]. Therefore, it could be a useful tool not only for determining the characteristics of increased risk of LS but also the effects of prolonged exercise intervention in middle-aged and older individuals.

Serum albumin

The age-related loss in skeletal muscle and other age-related diseases, which result in drastically reduced quality of life [13], are associated with inadequate nutrition. Therefore, nutritional factors might affect the risk of LS. Interestingly, we found that serum albumin levels are negatively correlated with the total skeletal muscle mass, measured by bioelectrical impedance analysis. Lower levels of serum albumin (<4.3 g/dL) were found to be a significant risk factor for LS [6]. In general, serum albumin is a marker of the nutritional condition [14], acts as an antioxidant [15], and is a plasma volume expander [16]. Moreover, a decline in albumin level is an effective predictor for elevated tumor necrosis factor-α (TNF-α) levels in older people [17]. Since inflammatory reactions play an important role in the development of age-related muscle weakness, known as sarcopenia, a lower level of albumin, accompanied by a chronic high systemic level of TNF-α, could be an important risk factor for LS. Collectively, a lower albumin level might be associated with a decline in skeletal muscle mass, muscle antioxidant capacity, and inflammatory factors. It also appears to be related to an elevated risk of LS. Thus, low serum albumin levels could be a potential predictor for LS risk. Interestingly, we found that a low serum albumin level could predict decreased efficacy of resistance training for muscle thickness in community-dwelling older people (unpublished results). Nevertheless, future studies should be performed to clarify the significance of serum albumin levels in predicting an increased risk of LS among middle-aged and older individuals.

DHEA-S

We have demonstrated that the prevalence of LS was higher in men with lower DHEA-S levels. (cutoff: 88 μg/dL) and that male subjects with LS exhibited lower muscle strength in knee extension [6]. These findings suggest that lower DHEA-S levels could predict a higher risk of LS in middle-aged and older men. DHEA-S is an endogenously produced sex steroid that has anti-aging effects. The circulating DHEA-S level declines significantly with age; the mean DHEA-S concentration at the age of 65 years is less than one-fifth of the mean DHEA-S concentration at the age of 20 years, according to cross-sectional [18] and longitudinal [19] studies. However, either low or high levels of DHEA-S predict a greater mortality risk in older women [20]. Moreover,

acute incremental submaximal treadmill exercise (up to 77% of the participants' predicted maximum heart rate) induced a significant increase in DHEA-S levels only in community-dwelling older women, regardless of their physical activity levels [21]. Collectively, the contribution of DHEA-S levels as a marker for LS risk and the possible sex-specific response to exercise suggest that the physiological significance of DHEA-S in women might not be as clear as that in men. Several longitudinal studies have demonstrated that 30% of individuals aged ≥ 65 years do not experience a decline in their DHEA-S level [22]. Thus, further research is needed to determine whether targeted DHEA-S supplementation would provide clinical benefits in preventing LS.

CONCLUSION

In summary, it is unclear whether blood parameters are a feasible tool for screening the at-risk adult population for LS. Some indicators, such as serum cystatin C, HbA1c, albumin, and the sex hormones, such as DHEA-S, seem to be beneficial as predictive screening tools during annual health checkups and for determining of the effect of exercise interventions on the risk of LS. Data regarding the association between blood parameters and LS is still limited. Nonetheless, the current understanding of the relationship between the risk of LS and blood parameters summarized in this review would be a useful screening tool for early diagnosis and treatment of the LS to minimize the negative effects of LS on our activities of daily life and quality of life. Additional studies are required to clarify the significance of blood parameters for predicting an increased risk of LS in middle-aged and older individuals.

CONFLICTS OF INTEREST

The authors have no potential conflicts of interest to disclose.

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