Kampo Medicine - Current Research

Kampo Medicine and Concept of Weak Constitution – Frailty, Locomotive Syndrome, and Sarcopenia

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Introduction

In recent years, terms such as frailty, locomotive syndrome, and sarcopenia have been proposed to embody the concept of "weak constitution." The author has long been occupied with the question: "Is there any concept equivalent to frailty, locomotive syndrome, or sarcopenia in traditional medicine, particularly in *Kampo* medicine?" In practice, concepts quite akin to these terms have been used in *Kampo* medicine, and treatments for such conditions are also found in *Kampo* medicine. In this paper, frailty, locomotive syndrome, and sarcopenia will first be briefly described. The *Kampo* medicine terms (or candidate terms) corresponding to these concepts will then be introduced and compared. We will thus discuss correlations and differences between *Kampo* medicine and Western medicine. Due to limited space, only representative examples will be cited. After these discussions, the author will point out unaddressed issues associated with *Kampo* medicine research in order to provide hints that may stimulate future advances in *Kampo* medicine research. At the unaddressed issues related to *Kampo* medicine research, we will first discuss issues related to quantification in traditional medicine and then consider issues related to the globalization of traditional medicine.

1. Summarization of the terms frailty, locomotive syndrome, and sarcopenia

The concepts of frailty, locomotive syndrome, and sarcopenia will first be briefly described. The term "frailty" is used in the field of geriatric medicine. This term indicates weak constitution, senile decay, and weakening or vulnerability. In short, it is used to describe aging-associated irreversible weakness. Frailty may also be used to describe the state in the senile period (a period of discrepancy between healthy life expectancy and mean life expectancy), which is characterized by reduced physiological reserve resulting in the outcomes such as vulnerability to stress, disturbance in activities of daily living, requirement of assistance with daily living, and likelihood of death.

The term "locomotive syndrome" is used in the field of orthopedics. Unlike the term "frailty," which is a broad concept encompassing physical, mental/psychological, and social aspects, the term "locomotive syndrome" is a narrower term confined to the fields of orthopedics and rehabilitation. It is used to indicate "a condition of restricted daily living due to reduction in mobility (walking, standing and sitting, etc.) arising from locomotor organ dysfunction, leading to need or imminent need of assistance with daily living." Locomotive syndrome was proposed as a new concept at the meeting of the Japanese Orthopaedic Association in 2007[1)]. Since this condition may show recovery in response to appropriate treatment, early diagnosis is considered to be of high value.

Moreover, the concept of "sarcopenia" was recently proposed to indicate aging-associated reduction in muscular mass and muscular strength[2)]. Sarcopenia is one of underlying diseases of locomotive syndrome, focusing on reduction in muscular mass and muscular strength. The term was coined based on the Greek words sarx (flesh) and penia (loss). Disturbed

walking/balance associated with sarcopenia can lead to aggravation of frailty.

Now that the differences among frailty, locomotive syndrome, and sarcopenia have been briefly described, we will begin a more detailed discussion of frailty, locomotive syndrome, and sarcopenia. According to Fried et al., frailty is defined as "A physiologic syndrome characterized by decreased reserve and resistance to stressors, resulting from cumulative decline across multiple physiologic systems, and causing vulnerability to adverse outcomes"[3]. The concept of "frailty" is easy to understand for clinical practitioners, but is difficult to define strictly. For this reason, the five phenotypes of frailty proposed by Fried in 2001 seem to be used frequently during clinical practice. The five phenotypes comprise (1) weight loss, (2) fatigue (subjective sensation of fatigue), (3) low energy expenditure (reduction in activity of daily living), (4) slow gait (weakening of physical capability [walking speed]), and (5) weak grip (reduction in muscular strength [grip strength]). Patients with at least three of these phenotypes are considered to have "frailty" and those with one or two phenotypes are considered "intermediate" or "pre-frail"[4]. Frailty is in essence a reversible condition in which normalcy may be restored if the appropriate intervention is used. For this reason, early detection of frailty in elderly individuals and subsequent appropriate intervention is expected to enable the maintenance and improvement of functions of daily living. Although the Japanese term "*Kyojaku* (虚弱) or weak constitution" may be used as a translation for "frailty," it cannot sufficiently express the diverse elements of frailty (i.e., weakness in the physical, mental/psychological, and social aspects). The Japan Geriatrics Society is thus exploring a more appropriate Japanese term as a translation for frailty to lead to widespread recognition of frailty and dissemination of the importance of its prevention. "Frailty" may be caused by a variety of factors, including not only locomotor organ disease and aging, but also disturbed cognitive function, nutrition, mental state, and socioenvironmental factors. Epidemiological studies have demonstrated a close association between frailty and cognitive dysfunction. Although the exact mechanism is unknown, it has been epidemiologically shown that early detection of cognitive dysfunction is important to prevent frailty. In order to avoid frailty, maintain and improve functions of daily living, appropriate interventions based on more accurate epidemiological data are desirable. An important issue for the future is the execution of appropriate screening tests at early stages of the condition.

Frailty is a broad concept encompassing physical, mental/psychological, and social aspects. Locomotive syndrome, on the other hand, is a concept used in orthopedics and indicates a condition of restricted daily living due to reduction in mobility (walking, standing and sitting, etc.) arising from locomotor organs dysfunction, leading to need or imminent need of assistance with daily living. Since this condition may show recovery in response to treatment, early diagnosis is considered to be of high value.

Sarcopenia is attributable to reduction in muscular mass, muscular strength, and physical capabilities, and is a condition that may underlie locomotive syndrome. It is a term that has been coined relatively recently by Rosenberg and indicates the "aging-associated reduction in muscular strength or senescence-associated decrease in muscular mass"[5]. The decrease in skeletal muscle mass is assessed using the skeletal muscle index (SMI), which is calculated by dividing the limb skeletal muscle mass (kg) by the square of height (m), i.e., limb fat-free soft tissue quantity (kg)/height (m^2). A SMI of 2 standard deviations (SDs) below the mean SMI of healthy individuals aged 18-40 years is often considered to reflect significant decreases in skeletal muscle mass[6]. In 2010, the European Union Geriatric Medicine Society and 4 European and international societies related to nutrition jointly established the European Working Group on Sarcopenia in Older People (EWGSOP), which proposed a definition for sarcopenia[7]. Based on this definition, a diagnosis of

sarcopenia can be made if there is decreased skeletal muscle mass (essential) and either reduction in muscular strength or locomotor function, or both, are present. The parameters assessed to diagnose frailty include attenuation of physical function and reduction in muscular strength. This indicates that sarcopenia is closely associated with frailty. The presence of sarcopenia is associated with dizziness, fall/fracture, and frailty in elderly individuals, and correlates closely with physical dysfunction and conditions requiring assistance with daily living[8].

2. The term "asthenic" was seemingly used in the early 20th century.

Concepts such as frailty, locomotive syndrome, and sarcopenia, which correspond to the Japanese term "*Kyojaku*" or "weak constitution" were already in use at the beginning of the 20th century in Western countries. In 1908, a publication in the journal *Lancet* used the term "asthenic constitution" to indicate the group of diseases causing "atonic habit of body" in the broader sense of the term. These conditions included floating kidney, gastroptosis, enteroptosis, nervous dyspepsia, and neurasthenia[9]. The term "asthenic" seems to have been a word that was prevalent in those days. This term was also used in the famous paper on body build and physical constitution typing by Kretschmer. Kretschmer described three types of body build: pyknic (stocky and rounded), athletic (with strong development of muscles and bones), and asthenic or leptosomatic (lean and narrow)[10].

3. What is the traditional medicine term corresponding to frailty, locomotive syndrome, and sarcopenia?

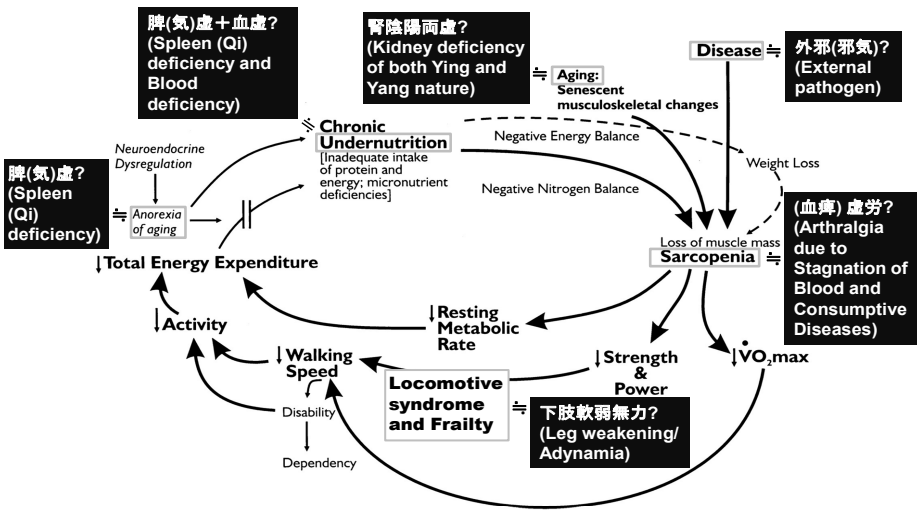
Before discussing *Kampo* medicine terms corresponding to frailty, locomotive syndrome, and sarcopenia, we will focus only on the physical aspects of frailty without considering the mental/psychological and social aspects mentioned in its definition to simplify the discussion. We will thus treat locomotive syndrome and frailty as the same concept and explore *Kampo* medicine terms corresponding to this concept.

The *Kampo* medicine or traditional Chinese medicine terms corresponding to locomotive syndrome and frailty seem to be "leg weakening/adynamia" and "weakening/adynamia," which were used in "*Dokkatsukiseito*, or Pubescent Angelica and Taxillus Decoction (*Du Huo Ji Sheng Tang*, 獨活寄生湯)" in the monograph "Important Formulas Worth a Thousand Gold Pieces (*Bei Ji Qian Jin Yao Fang*, 備急千金要方)"[11]. "Pubescent Angelica and Taxillus Decoction" is an Eight-Treasure Decoction (*Ba Zhen Tang*, 八珍湯) made of a Four-Substance Decoction (Si Wu Tang, 四君子湯) with blood-replenishing activity and a Four-Gentlemen Decoction (*Si Jun Zi* Tang) with *Qi*-replenishing (補気) activity. This herbal mix has been used to treat (1) conditions characterized by physical senescence (kidney deficiency according to traditional Chinese medicine); and (2) those condition involving shortages of *Qi* and blood accompanied by cold sensation and pain in the lower back and knees due to moisture or water retention, and by fear of coldness, pleasure with warmness, weak/powerless legs, and paralysis/neuralgia/swelling attributable to external factors (invasion by disturbing factors, such as wind, coldness, and moisture). In Japan, Pubescent Angelica and Taxillus Decoction is often replaced with an herbal extract called "Relax the Channels and Invigorate the Blood Decoction (Hu Jing Huo Xue Tang, 疎経活血湯)," which is covered by the national health insurance system.

The term corresponding to sarcopenia seems to be "Arthralgia Due to Stagnation of Blood and Consumptive Diseases (*Xue Bi Xu Lao*, 血痺虚労)," which is found in the Astragalus Decoction to Construct the Middle (*Ogikenchuto*, Huang Qi Jian Zhong Tang, 黄耆建中湯) or Minor Construct the Middle Decoction (*Shokenchuto*, Xiao Jian Zhong Tang, 小建中湯) in the monograph "*Kinkiyoryaku* (Essential Prescriptions from the Golden Cabinet, *Jin Gui Yao Lue*, 金匱要略)"[12]. This expression is found in the chapter "On Pulse, Symptom Complex

and Treatment of Arthralgia Due to Stagnation of Blood and Consumptive Diseases (血痺虚労病脈証并治)" in the same monograph. Both the Astragalus Decoction to Construct the Middle and the Minor Construct the Middle Decoction are herbal preparations used to treat consumptive disease (虚労). In traditional Chinese medicine, they are classified as *Onrikyokanzai* (agents used to reverse warmth and control coldness, 温裏祛寒剤). The concept of "decrease of skeletal muscle mass," which is used in the current definition of sarcopenia, was undoubtedly absent in the age of "*Kinkiyoryaku* (Essential Prescriptions from the Golden Cabinet)." However, patients with conditions corresponding to sarcopenia, i.e. patients with frailty presenting with decreased skeletal muscle mass, reduced muscular strength, or reduced locomotor function, are likely to have chronic disease or senescence as a background. The presence of chronic disease or senescence is probably accompanied by asthenia cold (Yang deficiency,陽虚). Therefore, the use of *Onrikyokanzai* (agents used to reverse warmth and control coldness), which is indicated for asthenia cold (Yang deficiency) is expected to be effective in patients with sarcopenia.

The author believes that aging corresponds to "kidney deficiency of both Ying and Yang nature (腎陰陽両虚)" (a concept of traditional Chinese medicine and Japanese *Kampo* medicine), while long-term malnutrition corresponds to the concept of "spleen (*Qi*) deficiency (脾(気)虚)" or "blood deficiency (血虚)." The author has compared these concepts using an illustration of the vicious cycle of frailty, locomotive syndrome, and sarcopenia, as proposed in the field of geriatric medicine in Western medicine[13] (Figure). This illustrative comparison includes some indefinite points. For example, reduced walking speed is a concept that began to be used when accurate measurements of time became possible and was absent in the age of "*Kinkiyoryaku* (Essential Prescriptions from the Golden Cabinet)." However, if "Symptom Complex of Arthralgia (痺証)" is present, a reduction in mobility should be present, and a reduction in walking speed is a plausible consequence. However, the author cannot rule out the possibility that new literature/documents will be found later indicating that a concept corresponding to reduced walking speed was used already in those days. This illustration is only the author's proposal and may require correction, improvement, and review in the future.



Adapted from Linda P. Fried et al. J Gerontol A Biol Sci Med Sci 2001;56:M146-M157

Figure: Cycle of frailty with *Kampo* terms: Under-nutrition, Aging, and Disease will lead elderly people to sarcopenia. And sarcopenia lead to loss of walking-speed, which is one of the frailty sign.

4. Existing issues essential to advancement of traditional medicine research

4-1 Quantification in traditional medicine

A striking difference in the diagnostic methods between *Kampo* medicine and modern medicine is that *Kampo* medicine basically attempts diagnosis and treatment through the comprehensive interpretation of subjective symptoms and objective findings or through holistic assessment of individual patients. One problem in *Kampo* medicine research that arises from this feature is difficulty in numerical or quantitative analysis when compared to Western medicine. However, quantitative analysis of parameters serving as criteria for diagnosis in traditional medicine will also be indispensable in the future. Surprisingly, there was little difference between *Kampo* medicine and Western medicine in the level of diagnosis/treatment until about 100 years ago, and the outcome of treatment for Spanish flu was better with *Kampo* medicine than with Western medicine. However, due to advances in science during the past 100 years, the predominance of modern medicine/Western medicine has been established. Following recent advances in technology used for measurements for medical use and in medical imaging technology, biochemical and diagnostic imaging data have frequently been used for diagnosis in modern/Western medicine. In contrast, in traditional medicine/*Kampo* medicine, the quantitative approach is seldom used, except for some sporadic cases wherein information regarding subjective symptoms obtained in interviews, questionnaires, etc., and physical findings (such as findings from abdominal investigations) is processed numerically. The methods used for quantitative analysis vary greatly among the different schools of traditional/*Kampo* medicine. In the latter half of the 1980s, Terasawa et al. made several attempts to quantitatively analyze diagnostic scores for *Qi*-Blood-Fluid[14] and similar tests. However, traditional/*Kampo* medicine is far behind the advanced level of modern medicine in the quantitative approach to diagnostic imaging and molecular biology.

In the future, it would be desirable to conduct comparisons and analyses of the correlations between quantitative data obtained in traditional medicine and data obtained in modern medicine regarding clinical indicators and biochemical markers. It would also be desirable to conduct pharmacological and molecular biological studies to enable the detailed visualization of biological activity and drug delivery at the molecular level so that further advances in traditional medicine research can be linked to life science research. Eventually, the development of diagnosis/treatment methods through the integration of modern medicine (Western medicine) and traditional medicine (*Kampo* medicine) beyond the borders of these two fields may contribute to further advances in medicine.

For example, we have introduced "New clinical assessment in diastolic heart failure: The correlation between a combination of clinical findings and indices with echocardiography"[15)16)]. We studied more than 30 outpatients at the hemodyalysis unit with simultaneous *Kampo*-scores and echocardiographical indices with echocardiography. They measured and compared *Kampo*-scores and echo-cardiographical indices by linear regression. According to our study, some of the *Kampo*-scores (*Suitai*-score (or water stagnation score)) had strong positive correlation to E/Ea (or E/e': transmitral early diastolic velocity / mitral annular early diastolic velocity ratio), which were suggested to have strong relation to pulmonary capillary wedge pressure (PCWP). They suggested that *Kampo*-scores especially *Suitai*-score could be used to define clinical assessment of congestion in hemodialysis outpatients with diastolic heart failure.

In order to address sarcopenia and the evidence in "Arthralgia Due to Stagnation of Blood and Consumptive Diseases" presented in the author's previous and present papers, we plan to collect not

only traditional medicine data from patients satisfying the diagnostic criteria for sarcopenia, but also data on biomarkers (e.g., inflammatory markers such as tumor necrosis factor-α and interleukin-6)[17] and imaging findings (computed tomography, magnetic resonance imaging, etc.). We will then study the correlations among these data. In addition, treatment of sarcopenia and "Arthralgia Due to Stagnation of Blood and Consumptive Diseases" using modern medicine will be compared to that using traditional medicine through randomized controlled trials (RCTs) if possible, or by means of cross-over trials if RCTs are not possible. We believe that diagnosis/treatment methods combining modern medicine (Western medicine) with traditional medicine (*Kampo* medicine) can be established through these incessant studies. It is desirable that such a scientific and objective version of traditional medicine be established as soon as possible.

4-2 Trends of globalization of traditional medicine

Differences in traditional medicine from different countries have been discussed at international conferences, such as meeting of the International Organization for Standardization (ISO; in particular TC249, which is discussed later) and the World Health Organization (International Classification of Diseases 11, etc.). However, smooth arguments have been hampered by conflicts of political and economic interest, honor/prestige of each country, and so on.

In 2009, China submitted an application for the establishment of the organization of an expert committee on traditional Chinese medicine (TC249) to the ISO in an attempt to facilitate the adoption of Chinese pharmacopeia and other domestic standards directly as global standards. If the standards proposed by China are adopted as global standards, Japanese pharmacopeia (now securing the quality of herbal medicines used in Japan from the viewpoint of Western medicine) and other standards related to herbal mixtures and *Kampo* preparations may have to be modified to match the Chinese domestic standards. Needless to say, a similar influence will also be seen in Korea, the U.S., and other countries in addition to Japan. At present, there is little international understanding of the differences between *Kampo* medicine in Japan and Chinese medicine. In addition, many individuals in Japan (other than healthcare professionals) believe that *Kampo* medicine in Japan is identical to Chinese medicine. However, the differences between *Kampo* medicine and Chinese medicine are as large as the differences between baseball and softball, and it would be impossible to apply the same rules to both these types of medicine. *Kampo* medicine in Japan is far behind Chinese medicine in terms of globalization effort. In addition, the education for non-experts in Japan is insufficient.

Conclusions

This paper briefly described frailty, locomotive syndrome, and sarcopenia, which are important problems in ultra-aging societies. The author then presented terms (or candidate terms) in *Kampo* medicine and traditional Chinese medicine corresponding to these concepts. This was followed by a comparison among these concepts and the description of some herbal preparations used for their treatment. The author also addressed existing issues essential to the advancement of traditional medicine research, focusing on the issues of quantification in traditional medicine and the globalization of traditional medicine. The author hopes to make some contribution to the stimulation of progress in traditional medicine research in the future.

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