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Integrative Medicine Research

journal homepage: www.imr-journal.com

Historical Review Article

Re-interpretation of traditional Asian medicine with constitutional perspective

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ARTICLE INFO

Article history:
Received 12 December 2012
Accepted 15 January 2013
Available online 26 January 2013

Keywords:
traditional Asian medicine
Sasang constitutional medicine
constitutional perspective

ABSTRACT

There has been a rapid increase in tailored medicine that emphasizes the complex inter-individual interactions, and this increase has paralleled recent significant achievements in genomics and Systems Biology. However, attempts to create a virtual human have been limited to low-levels of organization, such as gene-protein networks, due to the lack of systematic concepts at the higher levels of organisms (organ, individual, and environment). Constitutional perspective of various forms of traditional Asian medicine through the ancient, middle, and modern eras, particularly the holistic approach of Sasang constitutional medicine (SCM), may provide a novel framework for creating tailored medicine. This article aims to review the theoretical development of traditional Chinese medicine and the initiation of SCM in addition to summarizing current evidence on the genetic basis, bio-physiological features, and risk of disease of different SCM phenotypes. We also suggest that the patho-physiological principle and scientific evidence underlying SCM, particularly for the TaeEum type, can be effective in dealing with obesity-linked disease, which is a predominant disease in today's society.

1. Introduction

Ten years have passed since the Human Genome Project was completed in 2003; however, the sequencing of the human genome is just the initial step towards a full understanding and integration of DNA-based information into clinical practice.[1] Although reductionism is a useful method to understand the chemical and physiological basis of living systems, it is incapable of explaining how the system works and interacts with the internal and external environment.[2] Recent attempts using "*omic*" approaches (genomic, proteomic, and pharmacogenomics, among others), which refer to the mapping of multi-level interactions, and Systems Biology, which emphasizes living processes in their entirety, have provided better insights into the complex relationship between genotype and phenotype.[3] However, the inter-individual variations in inherited information and external traits are far from

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http://dx.doi.org/10.1016/j.imr.2013.01.001

understood and thus, individualized medicine has not yet been realized.[4]

In contrast, a complex approach that considers the human body as a whole with respect to its subtle relations with the environment has been used in various forms of traditional Asian medicine, such as traditional Chinese medicine (TCM), Kampo medicine (traditional Japanese medicine), Ayurveda (traditional Indian medicine), and Sasang Constitutional Medicine (SCM), which is a form of traditional Korean medicine. These "holistic" methods include several levels, the highest of which is the theoretical concept of *Yin-Yang* in TCM, *Sho* in Kampo medicine, *doshas* in Ayurveda, and *Sasang* in SCM, whereas lower concepts include fundamental substances and phenomena, such as *Qi*, *Blood*, *Body Fluid*, *pulse*, and *voice*...and so on.[5] With respect to constitutional traits, theoretical concepts and fundamental phenomena have been used for clustering and describing constitutional types, respectively. Although each system of traditional Asian medicine is equipped with different theoretical contents, the concept of the constitutional type is equivalent to the term "phenotype" in modern biology, which refers to variants in anthropometric features, personality traits, susceptibility to certain diseases, and response to external factors. However, the categorization used by TCM, Ayurveda, or SCM is not solely a categorization of the human being but is also a form of individualized medicine with various types of experiential evidence accumulated thorough their long history of practice.[6] Among the various forms of traditional Asian medicine, SCM appears to be the closest to a constitution-based medicine, in which treatment and prevention are tailored to the particular inherited (constitutional) types of each patient.[7] This review discusses the theoretical development of TCM and the initiation of SCM in addition to summarizing current evidence on the genetic basis, bio-physiological features, and risk of disease of different SCM phenotypes.

2. Trends in TCM over time and the initiation of SCM

The existence of two bibles of TCM, which are known as *Huang Di Nei Jing* (*The Yellow Emperor's Medicine Classic*) and the *Shennong Ben Cao Jing* (*Classic of Herbal Medicine*), dates the theoretical background of TCM back to ancient times (2500–2700 BC). Since this time, various practitioners of TCM have developed and completed this theory by employing their practical experience and interpretation. The most prominent physician in Chinese ancient times was *Zhang Zhong Jing* (150–219 AD), and he compiled the first practical textbook, entitled *Shang Han Za Bing Lun* (*Discourse on Fevers and Miscellaneous Illness*), which is a must-read classic for every TCM practitioner.[8] This book contains many formulae composed of Radix Ginseng, Radix Aconiti, and Cortex Cinamomi, which are medicinal herbs with properties of warming and reinforcing digestive function.[9]

However, it was not until the *Jin* and *Yuan* dynasties (1115–1368 AD) that the theory of TCM became well established due to the great contributions of the Four Great Schools, including *Liu Wan Su* (1120–1200 AD), *Zhang Cong Zheng* (1156–1228 AD), *Li Cao* (1180–1251 AD), and *Zhu Zhen Heng* (1281–1358). Although all used the *Huang Di Nei Jing* as their foundation, their academic ideas, clinical applications, and theoretical basis were completely different. *Liu Wan Su* insisted that the main causes of all diseases were Fire and Heat; *Zhang Cong Zheng* blamed external pathogenic factors for all health problems; *Li Cao* claimed that diseases originated from unhealthy digestive systems; and *Zhu Zhen Heng* emphasized the essential importance of Yin deficiency in pathogenesis. Thus, their priorities for therapeutics were different, such as Clearing Heat and Fire, Expelling External Pathogenic Factors, Reinforcing Spleen and Stomach, and Nourishing Yin. Their successors have developed these principles into "the Four Great Schools", which have remained significant to modern times.[10]

However, variations in the favored therapeutic methods of these four doctors may be explained from a constitutional perspective and with respect to the effect of the environment. *Liu* and *Zhang* lived in the northern region during the substantial era of the *Jin-Yuan* dynasties where people were physically strong and robust and had sufficient nutrition, whereas *Li* and *Zhu* lived in the southern region during the late era when famine was widespread and the population was weak and had vulnerable constitutions. Therefore, the aggressive therapeutic methods typically used by *Liu* and *Zhang* were effective for northerners, whereas the methods of replenishment used by *Li* and *Zhu* were appropriate for the southerners.[10]

Malnutrition and coldness were the main sources of health problems in ancient times, whereas diseases linked to poor hygiene were predominant in the Middle Ages. In contrast, sedentary lifestyles and high-calorie diets have been blamed for the increase in obesity-related diseases in modern times. Although a population may be exposed to the same environment, individuals may differ in their vulnerability to specific hazard factors. For example, those with an innately low resting metabolism may be at a higher risk for weight gain and cardiovascular diseases.[11] This inherited inclination was mentioned by *Lee Je Ma*, who invented SCM 100 years ago. According to SCM theory, humans may be categorized into four types: TaeYang (TY), SoYang (SY), TaeEum (TE), and SoEum (SE); these types differ in their physical and psychological attributes, disease susceptibility, and appropriate therapeutic methods.[12] From a constitutional perspective, *Lee Je Ma* showed that most of the formulae created by *Zhang Zhong Jing* in *Shang Han Za Bing Lun* are appropriate for SE individuals who inherit poor digestive function. He also noted that the formulae for SY individuals, who have an innate excess of *Heat*, are described superficially in *Shang Han Za Bing Lun* and are described in more depth by *Liu Wan Su* and *Zhu Zhen Heng*. Therapeutic principles and formulae for the TE type had not been mentioned until Lee Je Ma's era. He indicated that the TE individuals who are susceptible to weight gain should be treated by scattering and consuming Qi and nutrition and reinforcing respiratory function.[13]

3. Sasang constitutional perspective and scientific evidence

Several scientific reports of the inherited inclination in the SCM types have been accumulated with respect to

Table 1 – Scientific evidence of the traits of SCM types.

Reference	Publication year	Subjects	Constitution determining	Phenotype (genotype)	Results
The inborn genetic traits of the SCM types					
Lee et al.[14]	2007	Twin 731 pair All: 1462; TE: 373; SY: 434; SE: 655	QSCC II	Sasang constitution	Genetic influence (Totally 52%; TE: 48%; SY: 43%; SE: 47%)
Lee et al.[15]	2009	101 pedigrees All: 593; TE: 202; SY: 147; SE: 117	SCM professional	Sasang constitution	Heritability (TE: 55%; SY: 41%; SE: 47%)
Won et al.[17]	2009	A large family All: 40; TE: 26; SY: 2; SE: 8; unknown 4	SCM professional	Sasang constitution	Constitution-associated genetic loci (8q11.22-33, 11q22.1-3)
Kim et al.[18]	2012	All: 1222; TE: 512; SY: 389; SE: 302	SCM professional	Sasang constitution	Constitution-associated genes (TE: $n = 15$; SY: $n = 17$; SE: $n = 12$)
Kim et al.[19]	2012	All: 1222; TE: 512; SY: 389; SE: 302	SCM professional	Sasang constitution	Constitution-associated pathways and hub genes
Bio-physiological features among the SCM types					
Pham et al.[20]	2011	All: 911; TE: 366; SY: 332; SE: 323	Two SCM professionals	BMI and facial feature	TE: squarer face (men: longer eyes; women: longer jaw), BMI and facial metrics as good predictors
Pham et al.[21]	2012	All: 57; TE: 17; SY: 17; SE: 17	SCM professional	BMI, resting metabolic rate, cardiorespiratory fitness, and insulin sensitivity	TE and SE: association of BMI with health risk (cardiorespiratory fitness and insulin sensitivity); SY: association of BMI with increase in resting metabolic rate
Lee et al.[22]	2012	Healthy and BMI, 18.5-23 kg/m^2 TE: 9; SY: 9; SE: 10	Two SCM professionals	Gut hormone	PYY concentration: significant differences among three SCM types and higher in SE at post-prandial
Chae et al.[23]	2012	All: 245; TE: 60; SY: 63; SE: 102; unknown: 20	QSCC II	SPQ: behavior, emotionality, cognition	SPQ: different between SCM types; correlation with novelty seeking, harm avoidance, and extraversion
Park et al.[24]	2011	All: 98; TE: 41; SY: 31; SE: 25; TY: 1	Three SCM professionals	Temperament and character inventory	in temperament dimension, novelty seeking: SY > SE; harm avoidance: SY < SE
Pathological features among the SCM types					
Song et al.[25]	2012	All: 1.617; TE: 666; SY: 546; SE: 405	SCM professional	Metabolic syndrome	Odds ratio of prevalence (TE: 4.52; SY: 2.00; SE: 1.00)
Lee et al.[26]	2009	All: 1443; TE: 677; SY: 418; SE: 348	QSCC II and SCM professional	Diabetes mellitus	Odds ratio of prevalence (TE: 3.96; SY: 2.01; SE: 1.00)
Lee et al.[27]	2011	All: 1701; TE: 850; SY: 542; SE: 309	QSCC II and SCM professional	Hypertension	Odds ratio (TE: 1.37; non-TE: 1.00)
Choi et al.[28]	2011	All: 1535; TE: 755; SY: 480; SE: 300	QSCC II and SCM professional	Insulin resistance	Odds ratio of prevalence (TE: 1.43–1.49; non-TE: 1.00)
Cha et al.[29]	2011	All: 1218; TE: 826; SY: 215; SE: 177	QSCC II or SCM professional	BMI (*FTO* rs17817449 and*MC4R* rs17782313)	Enriched association signals of minor allele only in TE type
Song et al.[30]	2012	All: 1619; TE: 668; SY: 546; SE: 405	SCM professional	HDL-cholesterol and triglyceride (*APOA5* −1131T>C)	in TE and SY types: C carriers associated with increases in HDL-cholesterol and triglyceride
Song et al.[31]	2008	Women: 182; TE: 165; SY: 3; SE: 7	QSCC II	Obesity (*IL-1*α −889C/T)	Odds ratio of T carriers in TE: BMI<25 kg/m^2: 1.0; BMI 27-29 kg/m^2: 0.14
Lee et al.[32]	2008	Women: 181; TE: 165; SY: 3; SE: 7	QSCC II	Obesity (*IL-1*β +3953C/T)	Odds ratio of T carriers in TE: BMI<25 kg/m^2: 1.0; BMI 25-29 kg/m^2: 0.15
Um et al.[33]	2006	Women: 261; TE: 224; SE and SY: 17	QSCC II	Obesity (*IL-1ra* VNTR)	Marginal association of allele 2 carriers in TE
Lee et al.[34]	2007	TE: 128; SY: 87; SE: 47	QSCC II and SCM professional	Ischemic stroke (*PPAR*-γ Pro12Ala)	Odds ratio of Pro/Ala: 15-fold increase in TE

genetic basis on the inclination, cardiometabolic disease susceptibility, and bio-physiological features, such as anthropometric measurements (for body and face) and physiological responses (including psychological temperament) to external environments (Table 1).

3.1. *The inborn genetic traits of the SCM types*

The inheritance rate of the SCM types can be investigated using twin[14] and familial studies.[15] In a twin study performed using 731 twin pairs (monozygotic, 513 pairs; dizygotic, 218 pairs) and questionnaires, the SCM type for this study population was determined as 373 TE, 434 SY, and 655 SE (Questionnaire for the Sasang Constitution Classification II[16]). The genetic influence on the SCM type was 52%, which corresponds to the influence of complex and multifactorial traits; influences for each individual type were 48% for TE, 43% for SY, and 47% for SE[14]. In line with this study, a familial study employing clinical determination of the SCM types reported similar evidence for the heritability of TE, SY, and SE types: 55%, 41%, and 48%, respectively[15]. There were 101 pedigrees (all, 593; TE, 202; SY, 147; SE, 117) in the family investigated. Studies of the TY type are typically excluded because this type is too rare (frequency, 0.1–1%).

In addition to the heritable traits of the SCM types, genetic factors associated with the constitutional types have been determined using several genome-wide scan analyses. In a large family comprising 40 individuals (26 TE, 2 SY, 8 SE, and 4 unknown), 2 genetic loci, 8q11.22-23 and 11q22.1-3, were suggested to be significantly linked with SCM type.[17] Using the genome-wide association study (GWAS) and functional assessment via a text mining-based approach, constitution-associated genes have been identified, including 15 TE-associated, 17 SY-associated, and 12 SE-associated genes.[18] The combination of GWAS with a pathway-based analysis has led to suggestions that several pathways and hub genes that communicate with multiple pathways are distinctly related to SCM type.[19] Although the genetic factors identified from recent analyses of genome-wide scans appear not to address the heritable traits (41–55%) of the SCM types, it has been shown that the traits of the SCM types are genetically linked. Furthermore, the inherited inclination of SCM type for bio-physiological, psychological, and pathological traits may also be explained by the constitution-specific hub genes or genetic loci cross-talk between multilayered biological functions. Therefore, it is necessary to identify more robust genetic factors that are linked closely with constitutional type using genome-wide genotyping in additional large populations and/or resequencing using sufficient coverage.

3.2. *Bio-physiological and pathological features among the SCM types*

Recently, many researchers have reported that facial measurements, physiological status, and the levels of appetite-related hormones were different between SCM types. Using 2D images of 911 individuals, researchers found that facial measurements, such as area, width, height of lower part, and eye length, tended to be larger in TE types compared with other types. Interestingly, the body mass index (BMI) is positively correlated with facial measurements.[20] The relationship between BMI and physiological status estimated using the resting metabolic rate (RMR), cardiorespiratory fitness (CRF), and insulin sensitivity (IR) in young men was also constitution-specific.[21] Thus, BMI was positively correlated with RMR, which is one of the indicators of energy expenditure, only in the SY types, whereas it was negatively correlated with CRF and positively correlated with IR in the TE and/or the SE types only. With regard to appetite-related hormones, interestingly, SE-type individuals showed lower levels of anorectic gut hormones, such as peptide YY and glucagon-like peptide 1, after a meal, whereas TE types showed lower levels of orexigenic hormone (active ghrelin) before a meal, which may be due to the relatively high amount of energy stored in their body (higher BMI than other types).[22] Therefore, SE-type individuals may easily experience satiety after a meal and stop eating. As mentioned above, public health problems in modern society may be caused by diets that are excessively high in calories in addition to today's sedentary life. TE types with low satiety (low postprandial anorectic hormones) and low energy expenditure (low CRF and high IR) may develop adipose tissue, whereas individuals with high satiety and/or high energy expenditure, for example, the SE (high postprandial anorectic hormones despite low CRF) and SY types (high RMR despite low postprandial anorectic hormones), may resist fat accumulation. The different trends in energy expenditure between the SY and SE types may also be extrapolated from psychological temperaments, which are assessed using questionnaires; SY types tend to show more active behavior and easygoing personalities in the Sasang Personality Questionnaire[23] and have high novelty seeking and low harm avoidance scores in the Temperament and Character Inventory test,[24] whereas SE types show opposing behaviors.

These bio-physiological differences between SCM types affect the development of cardiometabolic disease. When the characteristics of individual SCM types are considered in the context of the modern lifestyle, TE types may be more susceptible to cardiometabolic diseases than the other types. Indeed, many scientific epidemiological reports indicate that the TE type may be a risk factor for disease development. In fact, the prevalence risks of metabolic syndrome[25] and diabetes mellitus[26] were increased the most in the TE type, followed by the SY type and the SE type. Additionally, TE types showed increased risk of disease susceptibility to hypertension[27] and insulin resistance[28] compared with non-TE types. Several genetic studies have supported these data. Polymorphisms in obesity-associated genes (fat mass and obesity associated; melanocortin 4 receptor) and of a lipid-associated gene (apolipoprotein A5) were associated with BMI in TE types[29] and with the levels of HDL cholesterol and triglyceride in the SY and TE types[30], respectively. Moreover, in several pilot studies, polymorphisms in interleukin-1 alpha, interleukin-1 beta, and interleukin-1 receptor antagonist were associated with obesity in TE women[31–33], and a polymorphism in the peroxisome proliferator-activated receptor-gamma was associated with ischemic stroke in TE types[34]. Taken together, TE-type individuals in modern society may carry a larger health burden, including obesity-related disease, than those with other SCM types. Therefore, recent efforts to elucidate causality and identify therapeutic regimens for treating cardiometabolic diseases may reveal solutions for each constitution type in constitution-based medicine, for example, the TE type of the SCM.

4. Perspectives

The pathological and physiological principles and herbal formulae in TCM have been developed through the ages for individuals who are especially vulnerable to particularly harmful environments. Problems bring forth solutions. Predominant diseases in certain eras have resulted in an abundance of medical theories and therapies focusing on those diseases.

SCM, which was invented by *Lee Je Ma*, is based upon the constitution, including individual variation in susceptibility to particular environmental conditions. The SE type, which is characterized by inherent weak digestive function, may be the phenotype that is the most vulnerable to food and clothing shortages. Malnutrition resulted in immune deficiency, and in ancient times, it was the main cause of mortality, in addition to widespread influenza-induced illnesses. These situations affect the SE type the most. In the Middle Ages, when infectious febrile diseases were common, SY-type individuals with innate excesses of Heat were the most vulnerable. Therefore, herbal formulae that were developed in ancient times with properties that stimulated digestive function and reinforced Yang-Qi were appropriate for SE type-specific illnesses, whereas those developed in the Middle Ages with Heat-clearing and Yin-reinforcing properties were appropriate for SY type-specific health problems.

In the modern era, in which high-energy foods and sedentary lifestyles are typical social problems, TE individuals, who are characterized by low metabolic rates, are the most susceptible to cardiometabolic diseases. Cardiometabolic diseases are induced by complex, multifactorial disorders. Therefore, these complications require a systems-based approach. SCM, in line with other Asian traditional medicines, is a form of systems-based medicine that focuses not on elements themselves but on their inter-relations. Systematic clinical data on body and facial features, personality traits, vocal types, and healthy physiological signs have been integrated into determining SCM type and prescribing therapies. Although research on SCM is in its infancy, a large number of studies have revealed that SCM types differ substantially in inherent physical, psychological, and genetic profiles and that the TE type is a risk factor for various obesity-linked diseases. It is plausible that those who are struggling with obesity and its complications, including diabetes and metabolic syndrome, have TE constitutions and that the therapeutic principles for treating this constitutional type, such as scattering and consuming Qi and nutrition, may provide a novel approach for the treatment of obesity.

Conflicts of Interest

No conflict of interest declared.

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