

The Pathophysiology Concept of Stress Ground State Drift and Its General Clinical Significance (Revealing the Modern Medical Laws Implied in the Core Theories of Traditional Chinese Medicine)

Abstract

This article defines the phenomenon that the neuroendocrine trunk NET activity (index) in the basic state continuously deviates from the median value within the normal range and is accompanied by corresponding characteristic manifestations as the Stress Ground State Drift (SGSD) (grade I), which is classified and graded according to causes, symptoms and indicators, and explains its formation mechanism, adding new content to the framework of classical stress theory, and proposing the diagnosis and intervention principles. The SGSD concept summarizes and explains the important essence of the concept categories of the core theories of Traditional Chinese Medicine (TCM), such as Kidney, Source-Qi, Yin-Yang, and the differentiation of Cold-Heat, Deficiency-Excess of Internal- Syndromes, and its relevance to the regulatory systems, such as Stress-Related Neuroendocrine Trunk (SRNET), thyroid and gonadal axes (HPT and HPG), and pathophysiology of Modern Medicine (MM), and then generally associated with many diseases, especially refractory diseases. In an effort to reveal the common pathological mechanism of MM "endogenous" diseases implied in the core theory of TCM, and the key scientific laws of its diagnosis and intervention, which should have important guiding significance for widely and effectively improving the efficacy of MM diseases. SGSD also has multiple important meanings as a link for the systematic "fusion" of TCM core theories into MM.

Keywords: Stress ground state drift • Stress pathophysiology • Neuroendocrine trunk • Basic theory of traditional Chinese medicine • Kidney • Source-Qi • Yin and yang • Cold and heat • Deficiency and excess • Syndrome differentiation

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Introduction

Modern Medicine (MM) still appears slow to improve the efficacy of many diseases, especially intractable diseases, which are often closely related to neuroendocrine (immune) network dysfunction. For example, the mechanism of autoimmune diseases is still unclear, and most treatments still rely on old immunosuppressive methods [1]. The biggest obstacles to related research should be: the basic theory of MM still has blind spots, clinical research methods and strict ethical restrictions, and animal experiments have technical and scientific value limitations. Turning our attention to the traditional medical system with a long history of experience to seek guidance or inspiration is a direction with less

resistance and promising prospects.

Research background\ Case structure

Status and characteristics of TCM: Among all traditional medicines in the world, the TCM system has the oldest and most detailed classics, and is the most prominent in terms of its scope of dissemination, application population and therapeutic effect [2]. Especially during the Covid-19 epidemic, it showed good results in the global fight against the epidemic [3]. Some scholars believe that if the United States had widely combined TCM method during the epidemic, the mortality rate could have been significantly reduced by at least 82.2%, and attributed it to poor communication with the government [4]. However, the scientificity and safety of its theories, diagnosis

and treatment methods have not been fully revealed and recognized, which may be more likely to be the key [4].

The outstanding effectiveness of TCM suggests that its theoretical system integrating ancient medicine and philosophy should imply scientific laws of disease mechanisms, diagnosis and treatment that MM has not yet recognized; and in-depth exploration and revelation of this law is obviously the correct direction for breakthroughs in the modernization research of TCM theory. However, the TCM system has significant features such as ancient Chinese language, ancient philosophy, experience, and certain non-objectivity, which have become major obstacles to understanding, learning, inheritance, and research, and therefore the stability, accuracy and safety of its diagnostic and therapeutic effects are also greatly affected. Therefore, the experts has realized that the way out for the development of TCM must be to "remove the rough and select the essence, remove the false and retain the true", be scientific and modern, and finally "fuse" into the MM system to promote the development of MM, and at the same time also promote the development of the TCM system itself [3].

Research progress on the modernization of TCM core theory: Although there have been many studies on the essence of the main terms of TCM core theory, such as "Source-Qi, Yin-Yang, Kidney-Yin-Yang, Cold-Heat, Deficiency-Excess", but the overall framework of the basic theoretical system is rarely touched. Classic essential research includes: the earlier studies on the nature of "Yin and Yang" and "Kidney-YA-D" have achieved fundamental results, namely, they are related to the Neuroendocrine Trunk (NET) components including HPA, HPT and HPG. In the past two decades, research has been deeply involved in the microscopic levels of cells, subcellular, as well as the omics such as proteins, metabolism and genes etc [5-7]. and molecular transduction mechanisms, but they are still in the category of essential research [7-10]. It is worth affirming and paying attention to these studies (including theoretical, laboratory and clinical research, etc.) for further modernization research and breakthrough progress in the framework of the TCM theoretical system, laying a foundation for basis or reference.

Stress theory and its current development status: The modern definition of stress is: when the stability of the body's internal environment is threatened, it produces non-specific or specific responses to internal and external stressors to maintain the body in a new steady state; non-specific stress NE

changes are mainly characterized by the excitement of the LC-SAM and HPA systems (i.e. SRNET), while cold stress, attack stress and sexual activity stress involving the HPT and HPG axes belong to specific stress [11-13]. In 1936, Han Selye proposed the concepts of stress and "non-specific reaction", and proposed the theory of "Systemic Adaptation Syndrome (GAS)", dividing GAS into three stages: alert stage, resistance stage and exhaustion stage, and established the basic framework of stress theory [14,15]. The subsequent progress in stress research has been mainly based on this framework, with continuous enrichment, refinement and micro-scale in terms of mechanisms and participating factors, and has involved the research and treatment of some stress-related disease mechanisms.

Importance and current limitations of TCM and stress studies: In the past two decades, TCM modernization research and stress research have gradually deepened to the molecular level and genetic engineering modeling. These studies undoubtedly help to continuously enrich our understanding of the microscopic mechanisms of stress and the details of the conceptual connotations of TCM [7-9]. However, in the macro level, especially in the modern research progress of TCM core theoretical system framework, it seems to be relatively slow. For example, the modern research conclusions on some basic concept categories of "Yin and Yang, Kidney Yin and Yang, Essence, and Source-Qi" and their disorders, and some of their essence are still not systematic enough, unclear and lack consensus, and the significance of these studies on the clinical (diagnosis and treatment effects) of MM is still relatively limited [9,10].

Essentially, stress is a physiological and pathological theory about the law of changes in NET activity. It can even be considered that different degrees of stress are frequent daily events. The NE network is the body's regulatory system, and the release of transmitters and hormones has a "biomagnification effect" (that is, the signal transduction link is amplified step by step to produce a high-efficiency effect; once the level deviates from the normal range, it will inevitably affect the normal function of the body). It is estimated that 75-90% of first-time internal medicine cases are related to stress, so stress research has become one of the most active fields in the world; and the above-mentioned TCM core concepts that are closely related to MM NE have always been the focus of TCM modernization research [12,16].

Analysis of the correspondence between the main functions of the TCM Kidney and the MM

regulatory system: The Kidney stores Essence and transforms it into Source-Qi (containing Source-Yin-Yang), regulates growth, development and reproduction, generates Marrow blood, which is the foundation of the internal organs (Viscera and Bowel), and metaplastic saliva, and for urine excretion, etc. It compares with the NE function of MM physiology, and combines with previous essential research, to make a comprehensive summary and inference: the above-mentioned functional essential meaning, except for urinary, is mainly consistent with the function of MM regulatory system NET hormones and transmitters; it is further speculated that "Essence" should correspond to NET neurons and endocrine cells [7,8,16-20]. Close to this, Shen Ziyin believes that Kidney essence corresponds to hypothalamic neural stem cells. "Source-Qi, and Source-Yin-Yang" corresponds to NET transmitters and hormones. "Viscera-Bowel (Zang-Fu) root" means that the kidney can regulate or influence other organ systems, and this is achieved through Source-Qi (containing Source-Yin-Yang). Yin and Yang are also the general principles of the Eight Principles, and their excess and deficiency reflect the basic laws of TCM pathogenesis, this article mainly involves "Internal syndrome Cold-Heat, Deficiency-Excess". The study of the essence of "Yin-Yang and the Kidney" has also revealed that it is composed of hypothalamus-pituitary-adrenal gland, thyroid gland, gonads, and autonomic sympathetic/parasympathetic entity components; for example the NE and energy metabolism levels of Kidney-YI-D are higher, while those of Kidney-YA-D are lower [5-10,17,18]. Therefore, the theory of Yin-Yang and Kidney disorder can correspondingly reflect the pathological mechanism of abnormal NET activity, that is, the pathophysiology mechanism related to stress; i.e., the SGSD concept proposed in this article to explain this mechanism [21].

Correlation and comparison between SGSD and related theoretical literature

This paper proposes that the concept of SGSD is closely related to the existing pathophysiological stress theory of MM and expands its theoretical framework. "Kidney, Source-Qi (containing Source-Yin-Yang) and their disorders, Cold-Heat and Deficiency-Excess Differentiation", as well as "Differentiation and Treatment" as the essence of TCM occupy a dominant position in the TCM system and are also the most distinctive part. The concept of SGSD is closely corresponding to the conceptual categories of these TCM core theories, and strives to clarify its implicit scientific connotation of MM mechanism. Previous literature on the essence of Yin-Yang has proposed several different views: for

example,

- "cAMP/cGMP", has now clarified that the main pathway of steroid hormones (including the core stress hormone GC) is to achieve genomic effects after binding to intracellular receptors, rather than the second messenger pathway;
- "Sympathetic/parasympathetic nerve";
- The correlation and correspondence between TCM Yin-Yang, Kidney-Yin-Yang and SAM, HPA, HPT and HPG axes;
- Homeostasis and compensatory homeostasis;
- Microscopic analogy study of Yin-Yang, such as cell growth regulation, gene transcription regulation etc.,

Manifestations of Yin-Yang at the molecular level [5-9,16,18,22-24]. These literatures have explained the scientific connotation of TCM Yin-Yang to a certain extent from different perspectives, but overall they still belong to the essential research and have not yet formed a MM concept or theory that can systematically correspond to the above-mentioned TCM core theory [25,26]. In particular, the concepts and essential expressions of Yin-Yang and Kidney-Yin-Yang are often ambiguous, while the research and revelation of the essence of Yin and Kidney-Yin is still relatively limited and the views are inconsistent [10,27,28].

The concept and theoretical hypothesis of SGSD

SGSD (Grade I) concept definition: In the body's basic state without obvious internal and external stressors and in a quiet state, the activity comprehensive indexes of non-specific stress LC-SAM- HPA, and specific stress HPT and HPG axes, which are within their respective normal range and continuously slightly deviate from their median values (defined as $\pm 20\%$), and correspondingly show more typical characteristic symptoms and signs, while excluding Neuroendocrine Quasi-Diseases (NEQD). The stress ground state with a higher comprehensive index is called positive drift (PSGSD), and the lower one is called Negative Drift (NSGSD); according to the different manifestations and causes, subtypes are divided into PSGSD1 and 2, NSGSD1, 2 and 3.

Referring to the manifestations and causes of Yin-Yang imbalance in TCM, SGSD is classified into types and subtypes:

- **Symptoms and signs:** PSGSD (Heat-

Syndrome): Fever, fear of heat, dry mouth or thirst, internal heat, hot flashes, night sweats, hot palms and soles, red tongue, yellow and dry tongue coating or little or no tongue coating, fast pulse [29,30]. NSGSD (Cold-Syndrome): poor spirit, fatigue, fear of cold, cold hands and feet, pale tongue, weak and slow pulse. PSGSD +NSGSD (YI-YA-D) has corresponding manifestations of both types.

- Causations:** PSGSD (Heat-Syndrome): higher ambient temperature, excessive intake of spicy and irritating food or "warming" herbs, strong or persistent negative emotional stimulation. PSGSD1 (Ex-Heat, YA-EX), short time, strong physique, "relatively insufficient" EN; PSGSD2 (D-Heat, YI-D): late stage of fever (such as infection, inflammation), long-term illness, excessive sexual activity, "absolutely insufficient" EN, old age, etc.

NSGSD: NSGSD1 (Qi-D): weak constitution, insufficient nutrient supply or absorption (insufficient intake, digestive dysfunction, anorexia, excessive weight loss, etc.), long-term illness or serious illness, long-term mental and physical fatigue, long-term lack of physical activity (disuse), old age, etc.; NSGSD2 (EX-Cold, YI-EX): shorter duration and stronger constitution, cold environment, long-term or excessive consumption of cold and cool food-drinks, excessive use of Cold herbs; NSGSD3 (D-Cold/YA-D): developed from NSGSD1, long-term illness, weak Yang or excessive

Yin in the constitution, frequent sexual activity and old age, etc., environmental and dietary causes are the same as NSGSD2.

Grade II and III SGSD: The comprehensive index value beyond the normal range belong to grade II SGSD (i.e., II YI-YA D-EX). Because the relevant indicators are "positive", they often overlap with many organic quasi-diseases of MM neuroendocrine, the latter of which is mostly caused by abnormalities in the structure of SRNET tissue cells or macromolecules at various levels, resulting in hypofunction or hyperfunction. SGSD is an extreme abnormality of comprehensive indicators, which is the depletion of Yin and Yang inTCM, that is the state of shock, organ failure or stress exhaustion in MM. SGSD: As above, the clinical manifestations are mild and distinctive [31]. Many of these important manifestations have been ignored by MM: such as dry mouth, dry eyes, cold hands and feet, sleeping sweat, hot palms and soles, poor spirits, fatigue, the soreness and weakness of waist and knees, etc., and the relevant indicators are all within the normal range, that is the SGSD level easily overlooked by MM clinically but is extremely important level. Because this type is mostly a functional change of NET, timely and effective intervention is critical for the timely prevention and treatment of various diseases. This article focuses on grade SGSD (hereinafter referred to as SGSD). It is worth emphasizing that the above classification and grading are essentially equivalent to TCM "Differentiation", that is, MM stratifies (classifies and grades) SGSD according to etiology, pathological nature, and severity (Figure 1).

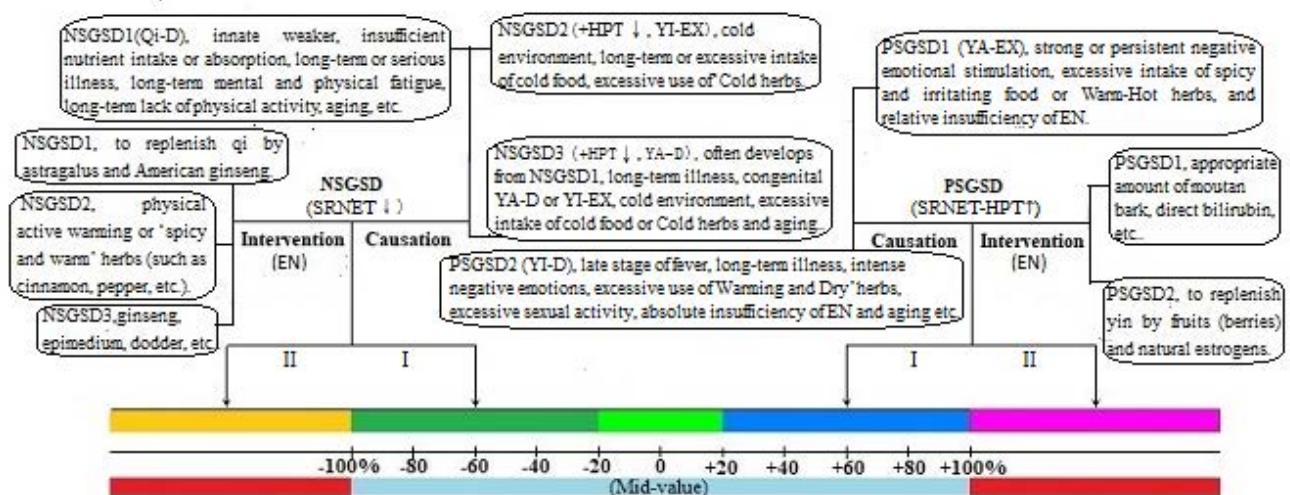


Figure 1: The figure shows the relationship between each type and grad 1 and 2 of SGSD (YI-YA, D-EX) and different mean percentage intervals, as well as their causes and intervention, and the corresponding NET ↓ changes. The horizontal axis is the mean percentage of the NET comprehensive index, with the zero point as the median (mid-value), the right side is positive, and the left side is negative.

Comprehensive indicators for discrimination (diagnosis)

- **Key manifestations (can be scored semi-quantitatively):** Fear of cold or heat, dry mouth (dry eyes), hot palms and soles; Pulse (P), Blood Pressure (Bp), little or no tongue coating; temperature of hands and feet (under an environment of 23°C, 30°C for hands and 27°C for feet are normal), fine core temperature (oral, axillary);
- **Laboratory tests indicators (complex):** 24-hour urine freecortisol; serum CRH, ACTH and CA(AD, NA, DA); thyroid series, sex hormone series, autonomic nerve function tests (skin scratch test, supine test, etc.), cardiac output and Basal Metabolic Rate (BMR), etc [14,16,29,30].

Justification of the SGSD concept

About the definition of SGSD (Level I): The viscera of TCM are mainly functional concepts, and the basis of dialectics is mainly symptoms and signs. In the temporary lack of large data sample statistics, referring to the definition of Basal Metabolic Rate (BMR) which is closely related to TCM Cold and Heat, and referring to the indicators of previous relevant literature to detect potential changes, the concept of SGSD is reasonably defined as the deviation of the relevant comprehensive index value from the median (mid-value) of its normal range by $\geq \pm 20\%$ [7,16,32-34].

As mentioned above, a comprehensive comparison of TCM and MM related theoretical concepts and reference to previous studies on the essence of TCM concepts suggest that: SGSD classification can correspond to TCM's the syndrome differentiation about Source-Qi and Yin-Yang imbalance, Cold-Heat, and Deficiency-Excess etc.; that is, positive drift indicates YI-D and YA-EX (Heat syndrome), and negative drift indicates Source-Qi-D, YA-D and YI-EX (Cold syndrome). According to MM stress theory, the above causes, in addition to innate deficiency, insufficient nutrient intake and absorption, aging and lack of exercise, are mostly stressors. For example, long-term illness and chronic diseases all contain certain stress components, and various pathological and uncomfortable symptoms should also be considered stressors. It can be seen that excessive or prolonged stimulation by different stressors can lead to a persistent state of mild hyperfunction or hypofunction of SRNET, that is, TCM's Source-Qi and YI-YA imbalance [12]. The SGSD concept uses the varied law of the basal state of SRNET activity from the baseline (median) to

describe the disorder, and is associated with the core theories of TCM, such as contents of Kidney, Source-Qi, Yin-Yang, the Eight-Principle SYND of Cold-Heat and Deficiency-Excess of Internal-Syndrome, and the SYND of Viscera-Bowel Yin-Yang imbalance (Figure 2).

Early classic literature on clinical and laboratory research test index data on Kidney-Ya-D, some of which showed "latent changes" (that is, the changes did not exceed the normal range and reached the positive standard), accounted for 11/47 and 12/47, etc. [7,32] Another clinical observation shows that not all indicators (17-OH) in patients with Kidney-YA-D are lower than normal values. For example, the positive (exceeding) rate of the indicators is only 60%-85%, and the endocrine axis HPA, HPT, and HPG also show scattered latent changes (That is, part of the index is still within the normal range), and the corresponding indexes are considered to be non-specific. Some scholars have earlier discovered that diurnal cortisol (GC) secretion in rheumatoid patients is at the lower limit of normal values. These studies also provide some stronger clinical supporting evidence for the rationality of defining SGSD the mean value of comprehensive indicators as mainly deviating from the median value within the normal range rather than exceeding the normal value range. The definition and classification of SGSD can reasonably explain the reasons why the indicators in the literature are latent and the positive rate is not high [33-35]. On the other hand, the latent or positive rate of HPA axis-related indicators is not high (20/48), which also suggests that in clinical practice, NSGSD (grade YA-D) seems to be more common. Even the micromorphological abnormalities of the hypothalamus and pituitary gland found in animal models also suggest that is quasi-disease level II YA-D, i.e. II NSGSD [23,28,36]. The animal models in the past literature seemed to be mostly produced according to the level of significant YA-D or Kidney-YA-D (level II), which is closer to the stress exhaustion type. It is speculated that its experimental research results and clinical correlation may be more likely to be distorted [8,10].

Compared with MM-related concepts such as homeostasis, basal metabolic rate, neuroendocrine immune network, sympathetic/parasympathetic nervous system, homeostasis and compensatory homeostasis, stress non-steady-state load, etc [18,24,37]. The concept of SGSD should be more in line with the above core concepts and theories of the TCM system; and can also be more comprehensively and systematically closely related to the MM stress theory, and then "fuse" the core part of the TCM theory with the MM

pathophysiology from the perspective of stress, and therefore be related to many diseases from the perspective of "different diseases with the same syndrome and the same treatment".

Essential analysis of SGSD (Figure 2)

Discriminating of the concepts of Source-Qi, Yin-Yang, and Kidney-Yin-Yang: The Kidney store Essence, and Essence transforms into Source-Qi (containing Source-Yin-Yang), Source-Yin-Yang is Kidney-Yin-Yang, and Qi-D is Source-Qi-D, Qi-D often develops into YA-D, and YA-D often coexists with Qi-D [17,29]. However, the definition of Kidney-

YI-D or YA-D "specifically refers to": Yi-D or YA-D plus the manifestations of soreness and weakness in waist and knees, genitourinary symptoms (including impotence, premature ejaculation, menstrual disorders or menopause, frequent urination at night). As mentioned above: The main essence of the Kidney is related to NE, and the essence of Qi-D, YA-D, and Kidney-YA-D has also revealed that they are (HPA+LC-SAM)↓, (HPA+LC-SAM+HPA)↓, and (HPA+LC-SAM+HPA+HPG)↓, respectively. It seems reasonable to conclude that YI-YA D-EX is Source-YI-YA D-EX [29].

Common syndrome types of the imbalance of Viscera-Bowel Yin-Yang in TCM	Key points of TCM SYND ^{29: 154-179}	SGSD				
		NSGSD		PSGSD		
		1(Qi-D)	2(YI-EX)	3(YA-D)	1(YA-EX)	2(YI-D)
		HPA-SAM↓	HPA-SAM-HPT↓		HPA-SAM-HPT↑	
*Kidney' YA-D	Cold and painful waist and knee, decreased libido, nocturia.					
*Kidney' YI-D	Weak waist and knees, tinnitus, spermatorrhea, menstrual disorders					
*Liver' YI-D	Dizziness, dry eyes, side pain.					
*Liver Fire' EX (hyperactivity)	Head and eye swelling and pain, side pain, irritability, tinnitus					
*Hyperactivity of Liver-YA	Head and eye swelling and pain, dizziness, tinnitus,					
*Liver and Kidney' YI-D	Side pain, dry eyes, weak waist and knees, dizziness,					
*Heart' Qi-D	Palpitations	+				
*Heart' YA-D	Pain in the precordial area			+		
*Heart' YI-D	Palpitations, upset, insomnia.					
*Heart Fire' EX (hyperactivity)	Insomnia, red tongue, mouth ulcers, nosebleeds.				+	
*Heart and Kidney' YA-D	Palpitations, weakness and coldness in waist and knees. limb swelling			+		
*Disharmony between the 'Heart and Kidney'	Upset, insomnia, sore waist and knees, tinnitus, nocturnal emission.			+		+
*Lung' Qi-D	Cough, wheezing, thin sputum.	+				
*Lung' Heat-EX (hyperactivity)	Cough, asthma, chest pain.				+	
*Lung and Kidney' YI-D	Dry cough, little phlegm, backache, spermatorrhea.					+
*Lung' YI-D	Dry cough, little or no sticky phlegm					+
*Spleen' Qi-D	Poor appetite, abdominal distension, loose stool.	+				
*Spleen' YA-D	Loose stools, abdominal distension, abdominal pain.			+		
*Spleen and Kidney' YA-D	Long-term diarrhea, morning diarrhea, cold pain in waist and knees.			+		
*Stomach Qi-D	Fullness in the stomach, dull pain that is relieved by pressure, poor appetite.	+				
*Stomach YI-D	Burning pain in the stomach duct, hunger without desire to eat.					+
*Stomach YA-D	Cold pain in the stomach			+		
*Cold stagnation in the stomach	Cold pain in the stomach, nausea and vomiting		+			
*Stomach Heat-EX	Burning pain in the stomach, rapid digestion, and easy hunge.				+	

Figure 2: The corresponding relationship between various SGSD types and TCM SYND of yin yang. Cold Heat and D-EX and common Viscera-Bowel Ying-Yang imbalance syndromes, as well as the corresponding relationship with higher and lower activity of each axis of SRNET. Higher and lower NET activity or function is indicated by ↓ and ↑.

Analysis of the nature of PSGSD1 and 2 (EX-Heat and D-Heat/YI-D) and Kidney-YI-D

The essence of PSGSD should be SRNET-HPT↑, in Kidney-YI-D it is SRNET-HPT-HPG T/E2 or P/E2 ↑. The essence of YI-D and KidneyYI-D has not yet been fully elucidated and a consensus has not yet been reached. The causes of the aforementioned PSGSD (YA-EX or YI-D) mentioned relative insufficient of essential nutrients (PSGSD1) or absolute insufficient (PSGSD2) [21,27,28]. There are 23 kinds of Yin-tonifying medicine commonly used in TCM, 16 of which are: protein (amino acid) and fatty acids such as donkey-hide gelatin, tortoise shell, turtle shell, black bean, black sesame; small berries such as cornus officinalis, raspberry, mulberry, schisandra chinensis, wolfberry, sea buckthorn; plant roots such as *Scrophularia ningpoensis*, *Ophiopogon japonicus*, *Asparagus cochinchinensis*, *Adenophora stellariae*, *Rehmannia glutinosa* [38,39].

- The main ingredients of these Yin-tonifying drugs mostly contain: a. multiple vitamins and minerals.
- High-valence proteins (collagen and keratin) containing multiple (Essential Amino Acids) EAA and (Essential Fatty Acids) EFA.
- Multiple (Plant Secondary Metabolites) PSM, such as small berries rich in flavonoids, polyphenols, anthocyanins and triterpenes, etc. and other nutrients, and the content of polyphenols and anthocyanins is positively correlated with chromaticity [40,41].

It is worth noting that almost all of them contain natural plant and animal estrogens, such as *Rehmannia glutinosa* (catalpol), mulberry (anthocyanidin, resveratrol), *Schisandra chinensis* (schizandrin A and B), as well as raspberry, cornus officinalis, wolfberry, *Ligustrum lucidum*, etc. The molecular structures of anthocyanidins and flavonoids are similar to estrogens, among them, PE are also antioxidants and other beneficial ingredients [42-46]. Analysis of the categories and ingredients of these Yin-tonifying drugs should help reveal the essence of Yin and Kidney-Yin, and can counterevidence part of their essence, that is, the above-mentioned "Essential Nutrients (EN)", including multiple vitamins and minerals, high-titer proteins (containing more and complete essential amino acids) and natural estrogens (plants and animals), and that may also include essential fatty acids, i.e. VMPE and EAAEFA, and PSM with multiple beneficial effects [47,48]. These nutrients

are necessary for the synthesis of cytoskeleton and functional proteins and biochemical processes (cannot be synthesized in the body), that is, the material basis (Yin) corresponding to cell function (Yang) [49].

Phytoestrogens have been found in the fruits (fruits, seeds) or roots of hundreds of plants. It is reasonable to speculate that the antioxidants that often coexist with vitamins and minerals in the aforementioned small berries also often act as phytoestrogens [40,45]. For example, flavonoids (including anthocyanins) are coloring components, and they themselves are easily oxidized to darken the color (often dark berries) [41,47]. For example, anthocyanidins belonging to flavonoids, resveratrol belonging to phenols, and iridoids (catalpol) belonging to terpenes etc., all have estrogen-like parts in their molecular structures. Therefore, the view of TCM that "black enters the Kidney" can be explained, suggesting that the corresponding dark fruit components have specific selectivity for NET, HPT, and HPG cells, and supplementing VMPE and PSM and EAAEFA is to replenish Yin or Kidney-Yin [45]. However, some studies deny the direct effect of PE as a plant antioxidant in the body, and it is more likely that it specifically intervenes in the oxidative stress response and free radical production. This view seems to reasonably explain the partial efficacy of PE in the body, that is, it has certain tissue cell selectivity and specific antioxidant effects. In addition, the parasympathetic nerves belong to Yin [48]. Their activity often increases during stress, which should have the effect of restraining nerves or inhibiting the excitation of NET [18]. The parasympathetic nerves and their central nuclei neurotransmitters play a role in the energy storage and repair process, and should be part of "Yin". In short, TCM "Yin" from the perspective of essential nutrients is VMPE and PSM and EAAEFA, and from the perspective of regulatory functions, it is estrogen (derived from nature and the body) and parasympathetic nerves and their central (including hypothalamus) related nuclei neurotransmitters (5-hydroxytryptamine, acetylcholine, etc.), and may also include conjugated bilirubin (see below), which together constitute the essence of TCM "Yin, Source-Yin and Kidney-Yin" [13,16]. These components constitute elements for nutrition, cell repair, antagonism or negative regulation of MEMS activity.

Plant fruits and vegetables, seeds, herbs (roots and tubers) are rich in VMPE, PSM and EAAEFA, which have special antioxidant protection and various nutritional effects on neuroendocrine, especially the hypothalamus and endocrine glands [40,45]. The relative importance of these essential nutrients

and active ingredients to different parts of NET is reflected in: hypothalamus, B₁, VC, B₁₂ and ω₃ fatty acids; pituitary gland, VD and VE; adrenal gland, VC, essential amino acids, pantothenic acid (can also inhibit adrenal gland overreaction) [40]. Plant-derived ingredients help regulate NE, reduce the risk of various diseases, and have beneficial effects on diseases [50,51]. As mentioned above, it is clear that natural foods and drugs contain complex beneficial components for neuroendocrine, so they can be used to intervene in NET quasi-diseases and indirectly in diseases of other systems [40]. However, due to the lack of corresponding theoretical support in MM, especially the basic pathophysiology, and the lack of understanding of the rules related to the selection of plant varieties, ingredients and functions for the adaptability of the individual NE state of the disease; so far, the use of natural plants to intervene in NE in the field of MM is still limited, and there is a certain degree of blindness, so the effect of the intervention may be significantly lower than expected. The theory proposed in this article should provide certain theoretical guidance, that is, selecting specific plant varieties or ingredients and dosages to match the specific SRNET activity status of different diseases is expected to achieve more ideal intervention effects.

PSM has multiple hydrogen bonds, ionic bonds and special structures, and can affect cell proteins as multi-target components in non-specific and specific ways. For example,

- The effects of polyphenols (containing one or more hydroxyl groups) and terpenes (containing conjugated double bonds).
- Non-specific regulation of proteins and biomembranes, such as PSM can form covalent bonds with transcription factors to regulate gene expression [49,52,53,54].
- Antioxidant effect.

Binding to cell ER with a structure similar to estrogen to exert specific estrogen-like effects. These characteristics of PSM also partially support the tissue-cell specific selectivity of the varieties of tonifying Yin and Kidney-Yin in TCM theory and the pharmacological rules implied. Also due to the biomagnification effect of regulating system hormones and transmitters, it is speculated that the non-specific multi-target overall efficacy of these ingredients on body cells is mainly reflected in neuroendocrine regulation, that is, Yin and Kidney-Yin tonification can affect other organs [49].

Conjugated bilirubin should also be considered as Yin: stress can trigger the production of reactive oxygen species in the body and cause oxidative stress.

Long-term elevated levels of stress-related hormones (such as GC) can lead to abnormal morphology and increased fragility of red blood cells; in addition, red blood cell production in the bone marrow is inhibited, and spleen clearance is increased, which promotes premature aging of red blood cells and hemolysis or apoptosis; and then, which can cause an increase in blood bilirubin series components, including indirect and direct bilirubin [54-56]. The pharmacological effects of Chinese medicine bezoar are central sedation, lowering body temperature (fever), anti-oxidation, and anti-inflammation. Its (conjugated) bilirubin content accounts for more than 40% of bezoar, which should be the main active ingredient of bezoar. The metabolic pathway of bile pigments is that liver cells secrete direct bilirubin into the intestinal feces and then reabsorb part of the bilirubinogen to form an enterohepatic circulation [39]. In addition, the liver secretes part of the direct bilirubin and releases it into the blood, and the blood content is at a level that is harmless to the body. It is speculated that conjugated bilirubin may be a supplementary component of the general stress-related NET feedback regulation. The above-mentioned effects of bezoar suggest that conjugated bilirubin may be as an indirect product of red blood cell destruction during stress, which should be able to feedback inhibit the stress response to restrain its overreaction and excessive destruction of red blood cells, and help antagonize and eliminate some negative effects of stress such as central excitement, elevated body temperature, excessive peroxidation and decreased immunity. Therefore, it seems that direct bilirubin can be classified as a component of antagonizing stress response, including the "Clearing Heat", i.e., antagonistic intervention for PSGSD1 in this article.

Analysis of the nature of NSGSD1 (Qi-D)

The nature of NSGSD1 (Qi-D) should be SRNET (LC-SAM-HPA)↓. The definition of Qi-D is insufficient Source-Qi, and the clinical manifestations are mainly poor spirit, fatigue and weak pulse [29]. The proportion of people with Qi-D constitution can reach up to 40%. As mentioned above: Source-Qi corresponds to NET transmitters and hormones; here, it is further believed that the essence of Qi-D is lower LC-SAM and HPA activity. Qi-D is different from chronic fatigue syndrome [57]. The latter has seven types of syndromes and Qi-D accounts for the highest proportion. Previous studies have shown that the essence of Qi-D includes decreased HPA axis activity, weakened cardiac function, decreased HPG and sympathetic nerve activity, and others etc., no consensus yet [58-61]. This article speculates that the persistent mild lower activity of the HPA and

LC-SAM is the key essence of Qi-D. Clinical and experimental findings show that insufficient GC in the body can easily lead to fatigue. It is known that GC can promote skeletal muscle and myocardial contractility and increase vascular tone, and ACTH and GC can maintain and promote the excitability of the central nervous system. This can explain the key essence of the main symptoms of Qi-D, such as lower spirits, fatigue and weak pulse [12,16]. Recent studies have shown that cortisol replacement can significantly improve skeletal muscle mass in elderly individuals (should often having Qi-D), which partially confirms this view [62]. In addition, because HPA and LC-SAM activities are often linked, they are particularly evident in stress responses: the secretion of CRH by the paraventricular nucleus of the hypothalamus has a close interactive promotion relationship with LC-SAM, ACTH and GC can also promote the production and release of adrenal medullary hormones, and the enhancement of myocardial function and vasoconstriction by GC is achieved through the "permissive" effect on catecholamines [13,16]. In addition, adrenal stress core hormones GC and catecholamines have been proven to produce specific performance benefits for skeletal muscle. Although thyroxine, testosterone, estrogen, etc., which represent the characteristics of HPT and HPG activity, can also promote skeletal muscle protein synthesis, and the decrease of sex hormones may be one of the key mechanisms of muscle loss and muscle weakness, but the definition of Qi-D does not include the manifestations such as fear of cold, cold limbs, slower heart rate, sore-weak waist and knees, and genitourinary symptoms etc., which are characterization of YA-D and Kidney-YA-D [63,64]. Therefore, NSGSD1 (Qi-D) in this article essentially excludes the corresponding NE components of the latter two, namely the decrease of HPT and HPG activity.

Analysis of the nature of NSGSD2, 3 (Cold-EX and D-Cold/YA-D) and Kidney-YA-D

Based on the classics and recent related literature, it is believed that the essence of EX-Cold, D-Cold/YA-D and Kidney YA-D is HPA-SAM-HPT↓ and the latter plus HPG (T/E2 or PE2)↓ respectively (Figure 2). NSGSD2 is a relative insufficiency of HPA-SAM-HPT activity, while NSGSD3 is a reduced activity (absolute deficiency). Both show HPA-SAM-HPT↓ and the same symptoms of chills and cold limbs. It is generally believed that the essence of YA-D is HPA-HPT↓. Previous classic studies on the essence of Kidney-YA-D also clearly point to the HPG axis, i.e. HPA-HPT-HPG↓. However, quite a lot of the corresponding NSGSD should belong to Grade II (for the same reason as above) [6-8,10]. This

article believes that the axis target glands involved in the essence of Qi-D (NSGSD1), YA-D, and Kidney YA-D are slightly different from previous literature (the changes in the activity of the LC-SAM axis seem to be largely ignored). The reasons are shown in (Figure 2). It is worth emphasizing that sex hormones, including T and E2, are closely related to the maintenance and promotion of skeletal muscle cell quantity and performance. The decrease of sex hormones in the elderly leads to the corresponding decline of skeletal muscle quality and quantity, especially the large muscle groups involved in the activities of the lower limb joints (hip and knee), which seems to explain one of the main symptoms of Kidney-YA-D, namely soreness-weakness and cold-pain of the waist and knees. Other manifestations are easy to understand [64,65].

PSGSD formation mechanism

PSGSD: (NET, EX-Heat, D-Heat/Yi-D); It is speculated to be caused by various reasons (as the above) leading to absolute (PSGSD1) or relative (PSGSD2) deficiency of VMPE and PSM or E2 in the body. For example: Typical perimenopausal symptoms are mostly based on YI-D (accounting for 49.23% or Kidney-YI-D, including "Liver/Kidney" YI-D and other concurrent syndromes (Figure 2): hot flashes, sleep sweat, hot palms and soles, fear of heat, menstrual irregularity or menopause, insomnia, bad mood (such as irritability, irritability, depression, etc.), these symptoms are consistent with PSGSD2 type of Kidney-YI-D and Liver-Kidney-YI-D (Figure 2) [66-68]. While, menopausal disorder or menopause is one of the typical symptoms of Kidney-D, so it is reasonable concept to base clinical SYND on imbalance of Kidney-Yin-Yang. The mechanism of the above symptoms is analyzed as: a. Central ERα (Estrogen receptor α) is densely distributed in the brain areas such as the cerebral cortex, hypothalamus, and hippocampus etc., ERβ is significantly distributed in the preoptic area, cortex, amygdala, striatum, etc. It is well known that these brain regions are involved in temperature regulation, emotions, and the initiation, conduction and integration of stress, etc. The above-mentioned symptoms occur when estrogen is greatly reduced during menopause, which also suggests that E2 should mainly play a negative regulatory role in the function of neurons in these brain areas [69,70]. Obviously, the ER binding of estrogen to neurons in these brain areas decreases, resulting in regional neurons tend to be excited and produce corresponding symptoms of the nervous system, that is, PSGSD2 type of Kidney-YI-D or Liver-Kidney-YI-D (Figure 2). Another E2 negatively regulates NET is the glutamate pathway: it has been

confirmed that glutamate is the main excitatory transmitter in the brain and critical for maintaining ideal energy levels and neuronal plasticity in most brain regions, where most cells express at least one kind of glutamate receptor. It is known that stress and increased GC (i.e. increased SRNET activity, referred to as PSGSD in this article) can promote increased glutamate release and transmission in specific cortical and limbic areas of the brain (including hippocampus, hypothalamus, striatum, etc.), and excessive increase in glutamate can produce exciting effects [71]. E2 can exert a certain antagonism to glutamate through the Mitogen-Activated Protein Kinase (MAPK) pathway and mediate the glutamate transporter in astrocytes (Glutamine transportor, GLT) promotes the absorption of glutamate and reduces the glutamate content in the internal environment, and inhibits neuronal damage [72,73]. It can be seen that estrogen can antagonize excessive glutamate content in specific brain areas and restrain its development excitability causes toxicity, and can subsequently downregulate SRNET activity; obviously, estrogen deficiency may cause increased excitability or activity in specific areas of the brain and NET, that is, PSGSD2, and corresponding symptoms appear.

Young men and women may also have symptoms of YI-D (PSGSD2). A survey of 2,043 cases showed that 15% of adolescents (15 years-19 years old) had YI-D (corresponding to PSGSD2); 8.6% of adults (20 years-59 years old) had YI-D (PSGSD2). Combined with the above analysis of the nature of YI-D, it is believed that: As mentioned above, the various stressors causes of PSGSD, especially the relative or absolute insufficiency of exogenous VMPE & PSM provided by fruits and vegetables for a long time, (such as B1, B2, folic acid, and especially including PE etc., insufficient nourishing neurons and inhibition of excessive neuronal excitation, etc.) [74]. It is reasonable to speculate that the central mechanism is similar to that of menopausal individuals and the above symptoms appear. In addition, except for amenorrhea, not every menopausal woman has obvious all the above symptoms, this may be attributed to the offsetting effect of the NSGSD state or to the maintenance of adequate individual balanced nutrition in healthier women [68].

NSGSD (Qi-D, EX-Cold D-Cold/YA-D): The loss of NETs should be the main part of the NSGSD mechanism. NSGSD1 (HPA-SAM↓, Qi-D): NSGSD2 (HPA-SAM-HPT↓, YI-EX): It is mainly due to the presence of long-term or excessive cold stressors (as the above). NET, especially HPT, is excessively depleted, and the activity is relatively

insufficient; NSGSD3 (HPA-SAM-HPT↓, D-Cold/YA-D): It is often developed from NSGSD1 (Qi-D), (causes, except for cold shock, are the same as Qi-D), SRNET-HPT is over- consumed by the corresponding stressor (such as cold, fatigue, excessive sexual activity, etc [9,10].), resulting in decreased activity (absolute deficiency) in non-stressed conditions. In various types of SGSD, in addition to various stress losses, the factors of insufficient nutrition and repair, such as congenital factors, long-term nutritional deficiencies such as excessive dieting, indigestion, and aging etc [7,75,76]; can all cause lower NET function. For example, clinically, patients with Kidney-YA-D (NSGSD) have axes↓such as HPA, HPT and HPG including T↓, E2↑ or T/E2↓, and delayed pituitary stimulation test response, which is consistent with the view of this article. However, previous literature seems to have ignored the subtle differences in the changes in NET axis activity between Qi-D, YI-EX, YA-D and Kidney-YA-D (such as different NE axis↓ and their relative and absolute nature), and especially ignored the extensive participation of LC-SAM (Figure 2). A careful distinction and understanding of these differences should facilitate the appropriate selection of medications and methods for more effective intervention [7,8,77].

Histological and microscopic changes of SGSD

Long-term stress during the compensatory period can lead to adrenal hyperplasia, and patients with various chronic diseases have obvious adrenal hyperplasia. SGSD describes that the basal activity of persistent SRNET is slightly higher or lower, the corresponding morphological changes should be mild hyperplasia or atrophy [12]. In the early years, adrenal atrophy was found in autopsy of patients with Kidney-YA-D; microscopic studies of animal models of YA-Dy showed a decrease in hypothalamic CRH cells and pituitary ACTH cells, adrenal atrophy, especially obvious thinning of the fascicular zone, which seems to belong to NSGSD [78,79]. YI-D and YA-EX (PSGSD2), NET tissue should be hyperplastic, but experimental animal models of YI-D show inconsistent results: endocrine index activity↑, but adrenal and thyroid glands tend to atrophy. It is speculated that this phenomenon should be that the model syndrome type is not simply YI-D, and it may be caused by excessive or prolonged application of the cause, resulting in "YI-YA-D" [80]. Microscopic studies have also revealed the corresponding genetic, protein and metabolic omics characteristics of YI-YA imbalance with SRNET changes [7,8,81].

SGSD impact on health and disease

Yin and Yang is the highest concept category in TCM, can summarize pathological rules and is also the general outline of the Eight Principles. The Kidney is the foundation of the human body and its main function is realized through the Source-Qi. Therefore, revealing the essences of the TCM core theory, (i.e. SGSD), such as the imbalance of the YI-YA and Source-Qi closely related to MM's NET, the SYND of Cold-Heat and D-EX of "Internal Syndromes", and the SYND of the YI-YA imbalance of the "Kidney and Liver" and other Viscera-Bowel, that is to explain the potential pathophysiological laws of the corresponding MM neuroendocrine dysfunction that have not yet been recognized [17]. The mutual influence of disease and stress should be fully valued, because various diseases contain stress factors to varying degrees, and may lead to internal environmental disorders to form secondary stressors. The imbalance of Source-Qi (containing Source-YI-YA) can affect the "Yin-Yang-Qi-Blood" of other organs, it can be considered that SGSD is also the NE background cause or basic factor of many diseases [12,17]. It also acts as a pathogenic factor or physical background to trigger or aggravate various diseases and affect their outcomes. That is, the "different diseases with the same symptoms" principle of TCM YI-YA imbalance. For example, the literatures shows clinical data on YI-YA imbalance (i.e. SGSD) and effective intervention based on regulating YI-YA for various diseases including Alzheimer's disease and Parkinson's disease [7,17,82]. The impact of SGSD should include: the continuous deviation (drift) of relevant transmitters and hormones from the ground state affects the functions of various organs, the higher or lower basal metabolism, the abnormal oxidative stress response, the mismatch between cell nutrition supply and functional activity, and the decrease or disorder of immunity. These links can further lead to pathological changes in various system organs and tissue cells, including the occurrence and development of tumors, autoimmune diseases, allergic diseases, cardiovascular diseases, diabetes and other diseases. In other words, many diseases involve stress-related neuroendocrine disorders or imbalances, and the key link should be the pathological mechanism of SGSD. In addition, according to the TCM theory of natural medicines and acupoint stimulation methods for the effective prevention and treatment of YI-YA imbalance, it is reasonable to infer that the same or similar principles and methods can also be used for intervention.

SGSD intervention

Herbs and EN: In the light of that the classic tonic prescriptions for Yin and Yang deficiency, such as Zuogui and Youguiyin prescriptions, Liuwei and Guifu Dihuang prescriptions, all contain Yin-tonifying drugs, (such as *Rehmannia* root, *Cornus officinalis*, *Lycium barbarum*, etc. i.e., EN in this article), the intervention of all types of SGSD, including qi deficiency, should be based on supplementing EN (berries or other fruits and vegetables, seeds (such as black beans and black sesame seeds) [83]. Then, different herbs, compound prescriptions, or other methods such as massage and acupuncture are selected according to the classification.

PSGSD1: Heat-clearing herbs can be used to directly antagonize NET \uparrow , such as moutan bark (containing polyphenols, one of the components of Zuoguiyin and Liuwei Dihuang prescriptions), gardenia (containing cyclopentadiene ether terpenes), and direct bilirubin can be used in appropriate amounts; which can inhibit the excitability of the central nervous system (the higher part of NET), and the first two contain PE b [39,45,84].

- **PSGSD2:** Only EN can be used (Such as fruits, vegetables and a moderate amount of small berries, tonifying Yin to clear D-Heat).
- **Kidney-YI-D(PSGSD2+HPG \uparrow):** For simplicity, EN can be used, such as cooked rehmannia, cornus officinalis, raspberry, mulberry, etc. (all containing higher content of PE), and for compound prescriptions, the Liuwei Dihuang or Zuoguiyin prescription can be used.
- **NSGSD1 (Qi-D):** Use astragalus and ginseng to Replenish Qi to promote HPA-LC-SAM activity.
- **NSGSD2:** For simplicity, physical methods or appropriate amounts of "Spicy and Warm" herbs (such as cinnamon, cassia twig, dried ginger, etc.) can be used to "actively increase temperature" [42].
- **NSGSD3:** Appropriate amounts of herbal medicine can be used to promote NET-HPT \uparrow (Replenishing Qi+Warming medicine, such as astragalus, ginseng, cinnamon, dried ginger, etc.).
- **Kidney-YA-D:** Simple prescriptions can be based on NSGSD3 and supplemented with herbs such as Epimedium and *Cuscuta australis*; compound prescriptions can be Jingui-Shenqi or Yougui-Yin Recipe.

According to the principle of "Yin and Yang mutual generation" in the above-mentioned classic formulas, attention should be paid to sufficient and appropriate supplementation of daily EN, that is, matching the nutrient material basis of cells with their functional activity [42,83,85]. It is worth emphasizing that the types and amounts of Chinese medicine and EN intake should be as accurate and precise as possible according to the classification and level of SGSD. For the intervention or treatment of SGSD and overlapping NET quasi-diseases, drug treatment in MM generally includes antagonists and hormone replacement agents; while for the intervention of SGSD, after the diagnosis of whether it is a NET quasi-disease, the above-mentioned Chinese medicines are still used to intervene or assist in regulating "Yin-Yang, Cold-Heat, D-EX", that is, to regulate NET, including the hormone-like effects of animal and plant medicines [31]. However, compared with the MM method, Chinese medicine has fewer side effects because its pharmacological effects are mostly multi-target and multi-level effects on NET. For example, it can play a regulatory role on the hypothalamus, which is the higher part of SRNET [7].

Intervention for SGSD in specific applications, because clinical SYND is generally combined with mixed syndromes, the prescription should generally take into account the Yin and Yang of other organs or "Qi, Blood, Phlegm, Dampness and Blood Stasis"; in MM, it may be to consider: infection, blood rheology, blood lipids, blood pressure, blood sugar, water and electrolyte balance, blood and urine routine, etc., as well as the functions and manifestations of various organs, and then, adopt the methods combining Chinese and Western medicine for the targeted treatment; which is a systematic "fusion" of Chinese and Western medicine. It should be emphasized that the clinical diagnosis of SGSD must be carefully differentiated or excluded from various NET organic diseases.

Generalized health management

On the basis of the three cornerstones (reasonable diet, proper exercise and psychological balance)

- **PSGSD:** PSGSD1, strictly prohibit spicy and irritating, fried and roasted food and Warming Hot herbs, as well as coffee, strong tea, alcohol, tobacco, etc.; manage emotions, meditate, etc. PSGSD2, actively treat various chronic diseases; moderate sexual activities.
- **NSGSD:** NSGSD1, avoid excessive mental and physical fatigue, combine work and

rest, pay attention to balanced nutritional intake, especially the intake of the three major nutrients with sufficient calories; scientifically control weight, avoid excessive weight loss; insist on appropriate intensity and form of exercise (benign stressor stimulation).

NSGSD2, pay attention to keeping warm and preventing cold, avoid eating and drinking cold and icy food and drinks and Cold herbs or products, and moderate sexual activities. If SGSD is combined with NET quasi-diseases, it should be actively treated to avoid delays. All types of SGSD should be paid attention to adequate daily intake of EN, especially VMPE and PSM.

Conclusion

- SGSD concept has strong corresponding support of the theoretical and literature in the core content of TCM basic theory, and also has multiple meanings as a link for the systematic "fusion" of TCM core theories into MM.
- Proposing SGSD corresponding to the core theory of TCM may expand the existing stress theory framework and reveal the important pathophysiological laws of the coexistence of MM various (endogenous) diseases implicit in the TCM system.
- According to the presence or absence of characteristic symptoms and signs, it provides a pathophysiological basis for MM diagnostics to try narrowing the normal range of clinically relevant test indicators, so as not to miss potential or pre-disease patients with SGSD as much as possible.
- SGSD intervention is not only to improve or eliminate these discomforts or signs, but also means regulating different SGSD types to trigger the mechanism that may generally improve the efficacy of diseases (including refractory diseases such as autoimmune diseases).

It is conducive to simplifying the complexity of TCM compound prescriptions, such as distinguishing between nutritional and pharmacological Chinese medicines in TCM prescriptions, and allocating the former to the balanced nutrition (including PE and PSM beneficial components in fruits and vegetables and implementation of health management; many of these ingredients seem to be classified as "unknown

essential nutrients". It should have guiding significance for simplifying TCM treatment with Chinese medicine. e. The SGSD grading proposed in this article divides the part overlapping with NET quasi-disease into SGSD, that is, Yin-Yang EX-D, which should have certain inspiration and guiding significance for making the TCM-related Yin- Yang laboratory and clinical research more detailed and precise. Many diseases (including refractory diseases) are affected by the disorder of the NE immune network, SGSD can at least partially explain the main causes and clues of the mechanism of these disorders, and put forward approximately clear directional effective intervention and regulation ideas to reflect its important clinical value.

The main inadequacy of this article is that it is based on the previous TCM core concepts, MM physiology and pathophysiology, stress and other related theories and literature, as well as small sample clinical practice, and theoretically propose the pathophysiological concept hypothesis of SGSD and its intervention, which needs to be further confirmed by adequate laboratory and large-sample clinical studies. Strategic suggestions for further research and verification: According to the definition, classification and grading of SGSD and the clear concepts of the core theory of TCM, to design research plans, such as SGSD classification, grading and its corresponding the levels Yin-Yang and D- EX, and use clinical objective indicators as much as possible to verify this hypothesis in detail.

Abbreviations (Sort by alphabetical order) and note

ACTH: Adrenocorticotrophic Hormone
 AD: Adrenaline
 cAMP/cGMP: Cyclic Adenosine Monophosphate/ Cyclic Guanosine Monophosphate
 CA: Catecholamines, including AD, NA, DA
 CRH: Corticotropin-Releasing Hormone
 D: Deficiency or deficient
 DA: Dopamine
 E2: 17- β - estradiol
 EAAEFA: EAAs EFAs, i.e. essential amino acids & essential fatty acids
 EN: Essential Nutrients, ERa and ERb Estrogen Receptor a and b
 EX: Excess or excessive
 GC: Glucocorticoids

HPA: Hypothalamic-Pituitary-Adrenal (cortex) axis
 HPG: Hypothalamus-Pituitary-Gonadal
 HPT: Hypothalamus-Pituitary-Thyroid
 LC-SAM: Locus Ceruleus Sympathetic adrenomedulla
 MM: Modern Medicine
 NA: Norepinephrine
 NE: Neuroendocrine
 NEQD: Neuroendocrine Quasi-Diseases, NET Neuroendocrine trunk
 NSGSD: Negative SGSD
 P: Progesterone
 PSGSD: Positive SGSD
 PSM: Plant Secondary Metabolites
 SAM: Sympathetico-Adrenomedulla
 SGS: Stress Ground State
 SGSD: Stress Ground State Drift
 SRNET: Stress-Related Neuroendocrine Trunk
 SYND: Syndrome Differentiation
 T: Testosterone
 TCM: Traditional Chinese Medicine
 VMPE: Vitamine mineral and plant phytoestrogen
 YA: Yang
 YA-D: Yang-Deficiency
 YI: Yin
 YI-D: Yin-Deficiency

Note

- Symbol \uparrow or \downarrow : neuroendocrine activity or indicators are higher or lower.
- SRNET: i.e. non- specific neuroendocrine trunk, including HPA, LC-SAM.
- NET: including SAM, HPA, HPT and HPG.
- EN: including VMPE, EAAEFA and certain PSM.
- The TCM terms or concepts in this article are in accordance with WHO standard terminology, i.e. "WHO international standard terminologies on traditional medicine in the Western Pacific Region." World Health Organization (2007).

References

- Coronel-Restrepo N, Posso-Osorio I, Naranjo-Escobar J, et al. Autoimmune diseases and their relation with immunological, neurological and endocrinological axes. *Autoimmun Rev.*16:684-692 (2017).
- Castiglioni A. A history of medicine. *Lond Routledge*, 99-100 (2019).
- Mei WF. On the international status and development direction of traditional Chinese medicine. *World Trad Chin Med.* 8-10 (2006).
- Li Q, Wang H, Li X, et al. The role played by traditional Chinese medicine in preventing and treating COVID-19 in China. *Fron Med.* 14:681-688 (2020).
- Kuang AK, Gu DG. Experimental study on Yin-Yang in TCM (VI) Analysis of the interaction between Aconite and Cinnamon in the Goldblatt and Skelton hypertension model. *Chin J Integr Trad West Med.* 18:164-166 (1988).
- Chen SK. The pioneering research on the integration of traditional Chinese and Western medicine in my country and its inspiration (Part 3)-Professor Kuang Ankun's "ice-breaking journey" in pioneering the "Yin-Yang Theory" of traditional Chinese medicine and the integration of traditional Chinese and Western medicine research. *Chin J Integr Trad Chin West Med.* 36:1285-1289 (2016).
- Shen ZY. Review of research on the nature of kidneys in integrated traditional Chinese and Western medicine. *Chin J Integr Trad Chin West.* 32:304-306 (2012).
- Zheng YL, Guo CR, Sun ZM, et al. Research progress on the biological basis of kidney yang deficiency syndrome. *China Trad Chin Med Sci Techn.* 26:318-319 (2019).
- Liang YH. Review and Prospect of the Research on the Nature of Cold and Heat Syndromes. *Chin J Integr Trad West Med.* 39:397-404 (2019).
- Ji L, Shen Q, Guo XD. Research progress on animal models and detection indicators of yang deficiency. *Chin J Compar Med* 31:138-145 (2021).
- Jiang CL. Current status and trends of stress medicine. *Military Med.* 47:641-645 (2021).
- Jiang CL. Stress Medicine(M). (Second Edition). Shanghai: *Shanghai Sci Techn Pre.* 34-36 (2021).
- Wang JZ, Qian RZ. People's Medical Publishing House. *Pathophysiol(M)* 3rd Beijing. 191-193 (2015).
- Yan J, Lu CL, Liu ZQ. (eds). Introduction to Modern Stress Theory (M). *Beijing: Sci Press.* 33-34 (2008).
- Selye H. A syndrome produced by diverse noxious agents. *Nature.* 138:32 (1936)
- Ni X, Chapter 11, Endocrinology, in Physiology(M). Wang TH, Editor. 9th edition. *Beijing: People's Med Publ House* (2018): 360
- Zheng HX, Yang Z. Basic Theory of Traditional Chinese Medicine. *China Tradit Chin Med Press.* 65-68 (2021).
- He FD, He Z, Yan XH, et al. Deciphering Yin and Yang: A study on the material basis of Yin and Yang in TCM physiological and pathological states. *J Clin Res Trad Chin Med* 11:43-45 (2019)
- Du FQ, Zhu YH. Neuro-immune-endocrine network from the perspective of yin and yang. *Res Integr Trad Chin West Med.* 13:341-345 (2021).
- Wang B, Ma JX, Ma HF, et al. Effect of Zuogui Pills on reproductive endocrine hormones in oligoasthenozoospermia rat model. *Chin J Sexol.* 26: 78-81 (2017).
- Shen ZY. Research progress and summary of kidney (continued). *Chin J Trad Chin Med.* 3:56-60 (1988).
- Goldberg ND, Haddox MK, Nicol SE, et al. Biologic regulation through opposing influences of cyclic GMP and cyclic AMP: the Yin Yang hypothesis. *Adv Cycl Nucleotide Res* 5:307-330 (1975).
- Lu DZ, Wo XD. Current status and thinking of the research on kidney yang deficiency syndrome. *J Zhejiang Chin Med Univ.* 3:399-401(2007).
- Fan XJ, Yu H, Ren J. Homeostasis and compensatory homeostasis: bridging western medicine and traditional Chinese medicine. *Curr Cardiol Rev.* 7:43-46 (2011)
- Marx JL. The Yin and Yang of Cell Growth Control: There is growing recognition that the development of malignant tumors may owe as much to the loss of growth inhibition as to a surfeit of stimulation. *Science* 232:1093-1095 (1986).
- Shi Y, Seto E, Chang LS, et al. Transcriptional repression by YY1, a human GLI-Krüppel-related protein, and relief of repression by adenovirus E1A protein. *Cell.* 67:377-388 (1991).
- Shan S, Yan XJ, Liu HN. Analysis of modern research on Yin deficiency. *World Sci Technol:Mod Trad Chin Med.* 20:1501-1505 (2018).
- Liu YF, Cai DF, Chen XH, et al. Effects of Zuogui Pills on hypothalamic monoamine transmitter content and weight growth in L-glutamate monosodium rats. *Chin J Integr Trad Chin West Med* 17: 673-675 (1997).
- Li CD, Fang CY, (eds). Traditional Chinese Medicine Diagnosis,(M) (New Century 5th Edition). *Beijing: China Traditional Chinese Medicine Press.* 128-130. (2021).
- Shen ZY, Wang WJ. Reference standard for syndrome differentiation of deficiency syndrome in traditional Chinese medicine. *J Integr Trad Chin West Med.* 10:598 (1986).
- Jameson JL. Harrison's endocrinology. 2010.
- Wang WJ, Shen ZY, Zhang XM, et al. Clinical and experimental study on the effect of kidney-tonifying method on the hypothalamic-pituitary-gonadal axis in elderly men. *J Trad Chin Med.* 4:32-32 (1986).
- Shen ZY. Thoughts and practice from the study of kidney essence to the study of syndrome essence-the research on integration of traditional Chinese and western medicine promotes a higher level of complementarity between traditional Chinese medicine and western medicine. *Shanghai J Trad Chin Med.* 34:4-7 (2000).
- Shen ZY. Research on syndromes and neuroendocrine immune network. *J Trad Chin Med.* 21:10-11(2003)
- Chikanza IC, Petrou P, Kingsley G, et al. Defective hypothalamic response to immune and inflammatory stimuli in patients with rheumatoid arthritis. *Arthritis Rheum* 35:1281-1288 (1992).
- Shen ZY. *Research on 'Kidney' (Sequel)* (M). First edition. Shanghai: *Shanghai Sci Techn Press.* 232-239.(1990)
- McEwen BS. Protective and damaging effects of stress mediators. *N Engl J med.* 338:171-179 (1998).
- Zhong GH, Yang BC, eds. Chinese Materia Medica (M) (Fifth Edition, New Century). *Beijing, China Traditional Chinese Medicine Press,* 385-415 (2021).
- Mei QX. (ed). Handbook of Modern Chinese Medicine Pharmacology and Clinical Application (M). 3rd Edition. *Beijing: China Medical Publishing House.* 798-827 (2016).
- Khalid W, Maqbool Z, Arshad MS, et al. Plant-derived functional components: prevent from various disorders by regulating the endocrine glands. *Intern J Food Prop.* 25:976-995 (2022).
- Feng XR, Hou YN, Zhang XX, et al. Research progress on berry juice processing technology and its functional ingredients. *Food Ind Sci Techn.* 12:334-340 (2018).
- Yan PX, Du BJ, Luo R. Research progress on hormone-like effects of traditional Chinese medicines[J]. *Chin J Trad Chin Med.* 29:531-534 (2014).
- WANG SY. Effect of catalpol on " glucose deprivation" cardiomyocyte injury based on estrogen receptor. *Chin Pharmacol Bull.* 2019:786-792.
- Shi Y, Hou BL, Wu SL, et al. Research progress on phytoestrogens. *Asia-Pacific Trad Med.* 11:172-176 (2019).
- Zhao Y, Zheng HX, Xu Y, et al. Research progress in phytoestrogens of traditional Chinese medicine. *J Chin Mater Med.* 42:3474-3487 (2017).
- Cai XY, Zhang ZJ. Research progress on the pharmacological effects of phytoestrogens and related traditional Chinese medicines. *Mod Chin Med Res Pract.* 34:75-78 (2020).
- Li CW, Wei YL. Research progress on the characteristics and application of phytoestrogens. *Genom Appl Biol.* 39:1264-1269 (2020).
- Shen YH, Chen CX. Research progress on anti-oxidative stress. *Chin Patent Med.* 2019; 41: 2715-19.
- Wink M. Modes of action of herbal medicines

- and plant secondary metabolites. *Medicines*. 2:251-286 (2015).
50. Slavin JL, Lloyd B. Health benefits of fruits and vegetables. *Adv Nutr*. 3:506-516 (2012).
 51. Arshad MS, Khalid W, Ahmad RS, et al. Functional foods and human health: an overview. *Funct Foods Phytochem Health Promot Potential*. 2021.
 52. El-Readi MZ, Eid S, Ashour ML, et al. Modulation of multidrug resistance in cancer cells by chelidonine and Chelidonium majus alkaloids. *Phytomedicine*. 15:282-294 (2013).
 53. Holtrup F, Bauer A, Fellenberg K, et al. Microarray analysis of nemorosone-induced cytotoxic effects on pancreatic cancer cells reveals activation of the unfolded protein response (UPR). *Br J Pharmacol*. 162:1045-1059 (2011).
 54. Obeagu EI, Igwe MC, Obeagu GU. Oxidative stress's impact on red blood cells: Unveiling implications for health and disease. *Medicine*. 103:e37360 (2024).
 55. Feng S, Tang D, Wang Y, et al. The mechanism of ferroptosis and its related diseases. *Mol Biomed*. 4:33 (2023).
 56. Stier A, Reichert S, Criscuolo F, et al. Red blood cells open promising avenues for longitudinal studies of ageing in laboratory, non-model and wild animals. *Exp Gerontol*. 71:118-134 (2015).
 57. Chen RD, Yang ZM, Lin YZ, et al. Investigation and analysis of 6525 cases of TCM constitution classification. *J Nanjing Univ Trad Chin Med*. 25:104-105 (2009).
 58. Wang Y. Neuroendocrine mechanisms of HPA axis and 5-HT system in patients with chronic fatigue syndrome and progress in traditional Chinese and Western medicine treatment. *Mod Dist Educ Trad Chin Med*. 143-146 (2016).
 59. Yu H, Sun L. Research progress on biochemistry and molecular biology of Qi deficiency syndrome. *Inform on Trad Chin Med*. 48-51(2005).
 60. Han B, Li BX, Li Z. Study on the relationship between changes in pulse chart, cardiac function, and blood rheology parameters and syndrome differentiation of qi deficiency and yang deficiency. *Chin J Trad Chin Med Pharm* 7:133-134 (2000).
 61. Shen WX, Liu YM, Liu XY. Using modern medical theory to clarify the nature and pathogenesis of Qi deficiency syndrome. *J Med Res*. 34:6-8 (2005).
 62. Prabakaran AD, McFarland K, Miz K, et al. Glucocorticoid intermittence coordinates rescue of energy and mass in aging-related sarcopenia through the myocyte-autonomous PGC1alpha-Lipin1 transactivation. *Biorxiv*. (2023).
 63. Steiner JL, Johnson BR, Hickner RC, et al. Adrenal stress hormone action in skeletal muscle during exercise training: An old dog with new tricks?. *Acta Physiol*. 231:e13522 (2021).
 64. Sipilä S, Narici M, Kjaer M, et al. Sex hormones and skeletal muscle weakness. *Biogerontology*. 14:231-245 (2013).
 65. Srinivas-Shankar U, Roberts SA, Connolly MJ, et al. Effects of testosterone on muscle strength, physical function, body composition, and quality of life in intermediate-frail and frail elderly men: a randomized, double-blind, placebo-controlled study. *J Clin Endocrinol Metab*. 95:639-650 (2010).
 66. Wang HB, Cui JM, Zhao S, Sun N, Zhang P, Shi YK. Correlation between Kupperman score and TCM constitution in menopausal women. *J Beijing Univ Chin Med*. 37:277-279 (2014).
 67. Du HL, ed., *Obstetrics and Gynecology of Integrated Traditional Chinese and Western Medicine(M)* (New Century Fourth Edition). Beijing: China Trad Chin Med Press. 219-292(2021).
 68. Wang DH. Clinical observation on the treatment of perimenopausal syndrome with integrated traditional Chin west med. *J Pract Trad Chin Med*. 39:910-912 (2023).
 69. Cao Y, Zhu H, Lu CM. Research progress on the effects of estrogen on the central nervous system. *Advan Anatomical Sci*. 23:538-540 (2017).
 70. Almey A, Cannell E, Bertram K, et al. Medial prefrontal cortical estradiol rapidly alters memory system bias in female rats: ultrastructural analysis reveals membrane-associated estrogen receptors as potential mediators. *Endocrinology*. 155:4422-4432 (2014).
 71. Pal MM. Glutamate: The master neurotransmitter and its implications in chronic stress and mood disorders. *Front Hum Neurosci*. 15:722323 (2021).
 72. Musazzi L, Racagni G, Popoli M. Stress, glucocorticoids and glutamate release: effects of antidepressant drugs. *Neurochem Int*. 59:138-49 (2011).
 73. Karki P, Smith K, Johnson Jr J, et al. Astrocyte-derived growth factors and estrogen neuroprotection: role of transforming growth factor- α in estrogen-induced upregulation of glutamate transporters in astrocytes. *Mol Cell Endocrinol*. 89:58-64 (2014).
 74. Wu CY, Luo WB, Wang NN, Xu Z, Li J, Wang Q. Epidemiological investigation of 2043 cases of TCM constitution in Jiangsu Province. *Chinese Journal of Basic Medicine in Trad Chin Med*. 138-140 (2009).
 75. Ma SY, Zhu M. Research progress on functional hypothalamic amenorrhea. *J Intern Reprod Health/Fam Plann*. 39:67-70 (2020)
 76. Zhang XM, Yao MY. Research progress on the treatment of diet-induced hypothalamic amenorrhea with traditional Chinese medicine. *Adv Clin Med*. 13:7847 (2023).
 77. Shen ZY. Research on the location of kidney yang deficiency syndrome. *Chin J Integr Trad Chin West Med*. 1:50-52 (1997).
 78. Qiu BG, Ning X. Progress in modern research on Yin-Yang theory. *Henan Medicine*. 4:33-36 (1981)
 79. Zhang LJ, Shen ZY, Cai DF, et al. Effects of epimedium on hypothalamic-pituitary-adrenal-thymus axis inhibition model in rats. *J Trad Chin Med*. 37:620-621 (1996).
 80. Zhang GL, Hu WH, Meng FM. Pharmacological study on Pingdianling No. 1 prescription. *Experim Anim Compar Med*. 16:179-181(1996)
 81. Pan XJ, Lou BC, Zhu YT. Preparation method of kidney yin deficiency model and research progress of kidney yin deficiency syndrome. *New Chin Med*. 3:23-27 (2019).
 82. He WB, Guo L, Zhang JL. Research on the mechanism of different diseases with the same syndrome in brain degenerative diseases based on Yin-Yang and system theory. *Chin J Trad Chin Med*. 28:873-876 (2013).
 83. Li J, Zuo ZY. (eds). *Pharmacopoeia(M)* (Fifth Edition in the New Century). Beijing: China Trad Chin Med Press. (2021)
 84. Cai CJ, Zhang ZL, Zuo YM, et al. Study on the chemical components of iridoids in *Gardenia jasminoides*. *Lishizhen Trad Chin Med*. 2:342-343 (2013).
 85. Zhong LY, Shen ZY, Cai DF, et al. Effects of three types of compound formulas that nourish the kidney, strengthen the spleen and activate blood circulation on the hypothalamus-pituitary -adrenal-thymus axis and CRF gene expression. *Chin J Integr Trad Chin West Med*. 1:39-41(1997).