Cellular and Molecular Biology
E-ISSN : 1165-158X / P-ISSN : 0145-5680
www.cellmolbiol.org

Targeting FoxO1 in traditional Chinese medicine for the treatment of diabetes

Yang Liu[1*], Bingmei M. Fu[2*], Ye Zeng[3*]

[1] The Hong Kong Polytechnic University, Hung Hom, Kowloon, Hong Kong
[2] Department of Biomedical Engineering, The City College of the City University of New York, New York, USA
[3] Institute of Biomedical Engineering, West China School of Basic Medical Sciences and Forensic Medicine, Sichuan University, Chengdu, Sichuan, China

ARTICLE INFO

Mini Review

Article history:
Received: May 11, 2023
Accepted: October 28, 2023
Published: November 30, 2023

Keywords:

FoxO1; diabetes; traditional Chinese medicine (TCM); mapping; signaling molecule

ABSTRACT

Traditional Chinese medicine (TCM) encompasses treatment strategies for diabetes, which is referred to as "Consumptive Thirsty" syndrome. Recently, there has been a discovery regarding the mapping between TCM and signaling molecules, which has revealed a remarkable consistency between TCM and modern medicine from a molecular perspective. In this manuscript, we have summarized the etiology and treatment strategies for diabetes in TCM and have examined these strategies in the context of molecular mechanisms. Our review demonstrates that the targeting molecule of TCM for the treatment of diabetes is FoxO1, a transcription factor that plays a pivotal role in regulating gluconeogenesis and glycogenolysis. TCM ranks the development of diabetes into three stages and utilizes different herbal formulas to control FoxO1 accordingly. At Stage 1, TCM inhibits FoxO1 by lowering its expression in the lung. At Stage 2, TCM increases the expression of FoxO1 by suppressing its activity in the stomach. At Stage 3, TCM utilizes the famous herbal formula Liuwei Dihuang Pill to amplify the expression of FoxO1, and to enhance the concentrations of potassium, phosphorus, and Wnt, but to reduce the concentration of calcium. These TCM treatment strategies are in accordance with corresponding mechanisms in modern medicine.

Doi: http://dx.doi.org/10.14715/cmb/2023.69.12.8

Introduction

Traditional Chinese medicine (TCM) has been utilized in China and other East Asian countries for thousands of years. The fundamental doctrinal source for TCM is "Yellow Emperor's Inner Canon" (YEIC). According to YEIC theory, vital substances within the human body, such as Qi, Yang Qi, Yin Qi, among others, regulate physiologic and pathological processes. TCM diagnosis and treatment strategies have been based on the functions and interactions of these vital substances. The YEIC framework also provides insights into the treaments of diabetes by TCM vital substances (1).

In modern medicine, molecular signaling represents a fundamental physiological process. Signaling pathways encompass a series of chemical reactions that occur within the cytoplasm of a biological cell in response to a stimulus, also known as a first messenger. This stimulus interacts with a receptor, which then transduces the signal to the cell interior through second messengers, ultimately leading to amplification and transfer of the signal to effector molecules. This series of biochemical events often occurs in a linear cascade, where one event triggers the next. Throughout the signaling cascade, various regulatory factors are involved at each step to tightly control and modulate cellular responses, allowing cells to effectively respond to the cues from their changing internal and external environments (2).

Recently, mappings between TCM and signaling molecules have been uncovered, and the mappings between TCM vital substances and signaling molecules have been compiled and presented in Figure 1 and Table 1 for reference. In the book titled "The Mapping between Traditional Chinese Medicine and Signaling Molecules" (3), it is illustrated that there are correlations between vital substances in TCM and signaling molecules in modern medicine. Both TCM and modern medicine elucidate physiological processes in the human body, albeit utilizing different terminologies. In each TCM vital substance and signaling molecule mapping, the physiological functions remain consistent. Moreover, the interconnections among various TCM vital substances correspond to the signaling pathways of relevant molecules. Likewise, specific TCM herbal medicines elicit similar effects on both the TCM vital substance and its corresponding molecule. By utilizing these mappings, one can scrutinize the TCM etiology of arthritis, diabetes, and constipation, and their related TCM therapeutic approaches. The analyses disclose the similarity in disease causation and management between TCM and modern medicine (3). In this review article, we present a summary of the etiology and treatment approaches for diabetes in the context of TCM. The information has also been translated into molecular terms to facilitate a deeper understanding of the topic.

Effect of Forkhead box protein O1 (FoxO1) on Diabetes

In TCM, the term "Consumption" corresponds to the

* Corresponding author. Email: yang.liu@connect.polyu.hk; fu@ccny.cuny.edu; ye@scu.edu.cn

Table 1. The mapping between TCM vital substances and signaling molecules (3).

TCM Vital Substance	Signaling Molecules	TCM Vital Substance	Signaling Molecules
Essence	Tyrosine	Liver Qi	Glutathione (GSH)
Mind	Melatonin	Liver Yin	Superoxide dismutase (SOD) Renin
Ethereal Soul	Serotonin	Liver Yang	Hepatocyte growth factor (HGF) Erythropoietin (EPO)
Corporeal Soul	Cysteine	Heart Qi	Magnesium (Mg)
Ideation	Tryptophan	Heart Yin	Angiotensin
Will	Arginine	Heart Yang	IGF
Thin Fluid	Proteins	Spleen Qi	Ghrelin
Thick Fluid	Lipids	Spleen Yin	Aldosterone Retinoic Acid
Qi	Sodium	Spleen Yang	Atrial Natriuretic Peptide (ANP)
Zong Qi	Dopamine	Lung Qi	Hypoxia Inducible Factor (HIF)
Nutrient Qi	Cyclic adenosine monophosphate (cAMP)	Lung Yin	Ascorbic Acid
Glory Qi	Adenosine triphosphate (ATP)	Lung Yang	Vascular endothelial growth factor (VEGF) Fibroblast Growth Factor 7 (FGF7)
Defending Qi	Chloride	Kidney Qi	Nitric Oxide (NO)
Yin Qi	Potassium	Kidney Yin	Wnt
Yang Qi	Calcium	Kidney Yang	Calcitonin Parathyroid hormone-related protein (PTHrP)
Clear Qi	Toll-like receptor 4 (TLR4)	Cold	Interleukin-1 (IL-1)
Turbid Qi	Leptin	Damp	Interleukin-6 (IL-6)
Righteous Qi	Immunoglobulin G (IgG)	Wind	NF-κB
Evil Qi	Lipopolysaccharide (LPS)	Heat	TNF-α
Stomach Qi	Amylase	Dry	Interleukin (IL-8)
Genuine Qi	Phosphorus	Summerheat	Cyclooxygenase-2 (COX-2)
Blood Qi	Iron	Consumption	Forkhead Box O1 (FoxO1)
Essence Qi	Zinc	Central	Aldosterone
Indulged Qi	Gonadotropin hormone-releasing hormone (GnRH)		
Mind Qi	Thyroid Hormone		

vital substance Forkhead box protein O1 (FoxO1) (3). FoxO1 is a transcription factor that assumes pivotal functions in modulating gluconeogenesis and glycogenolysis via insulin signaling pathways. Additionally, it participates in dictating the course of preadipocyte differentiation toward adipogenesis (4). Importantly, the TCM syndrome known as "Consumptive Thirsty" aligns with diabetes (3).

Insulin resistance, obesity, and inadequate insulin secretion represent the most commonly encountered etiologies for type 2 diabetes (5). FoxO proteins play a crucial role as targets in mediating the action of insulin, with the inhibition of FoxO1 being essential for both direct (hepatic) and indirect effects of insulin on hepatic glucose production and utilization. Additionally, when liver FoxO1 activity is disrupted, the extrahepatic effects of insulin are sufficient to sustain normal hepatic and whole-body glucose metabolism (6). The overexpression of FoxO1 protein in the liver enhances hepatic glucose output, and FoxO1 is among the factors that stimulate glucose production in this organ (7). In contrast to other body tissues, FoxO1 works differently in muscles. Following prolonged fasting, FoxO1 increases, and it attaches to a specific part of a gene called "pyruvate dehydrogenase kinase-4". This causes a substance called "pyruvate" to turn into "acetyl CoA" and speeds up the use of glucose. (8).

Activating FoxO1 in the kidney has the potential to prevent complications related to diabetes. Studies conducted both in cells outside of the body and in living animals have shown that in diabetic mice, the FoxO1 protein is reduced when kidney cells are exposed to high levels of glucose. In diabetes, FoxO1 can be affected in both the cytoplasm and the nucleus of cells. High blood sugar can increase the production of a protein called TNF-α in the kidney. This protein, in turn, boosts the levels of a molecule called STAT1, which prevents FoxO1 from functioning in the nucleus. Moreover, high levels of glucose in kidney cells can trigger a cascade of reactions called the AKT pathway, which breaks down FoxO1 (7, 9). Researchers believe that FoxO1 can protect kidney tissue by decreasing oxidative stress. Studies have indicated that when FoxO1 is overexpressed in kidney tissue, it increases the activity of genes that produce antioxidant substances, such as catalase and superoxide dismutase (SOD), which can help fight diabetes-related kidney damage (7, 10). Many studies have shown that using FoxO1 can be helpful in treating obesity and diabetes that depend on insulin (11). The role of FoxO1 in diabetes is succinctly depicted in Figure 2. Insulin effectively suppresses FoxO1, while Akt phosphorylates it. In the liver, FoxO1 facilitates glucose production, whereas in the kidney, it may mitigate compli-

Figure 1. The mappings between TCM vital substances and signaling molecules (3).

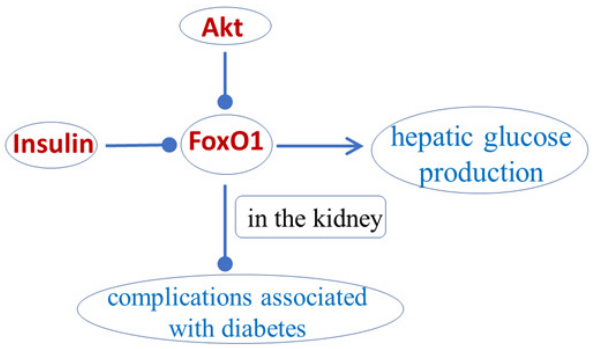

Figure 2. FoxO1 has a significant impact on diabetes. Insulin effectively inhibits FoxO1 while Akt phosphorylates it. FoxO1 promotes glucose production in the liver, while in the kidney, it could prevent complications linked to diabetes. The arrow indicates increasing, and the solid circle indicates inhibiting effects.

cations associated with diabetes.

TCM Treatment Strategies for Diabetes

Wansu Liu (1100-1180) was a renowned TCM practitioner during the Yuan Dynasty. He authored the book "Three Consumptions Theory" (12), which introduced the concept of "Consumptive Thirsty" Syndrome, also known as diabetes. Similarly, Danxi Zhu, another famous TCM physician of the Yuan Dynasty, wrote: "Danxi's Mastery of Medicine" (13), which presented the treatment strategy for "Consumptive Thirsty" Syndrome (diabetes). They classified the syndrome into three stages, with each stage corresponding to a specific organ: Stage 1 is linked to the lungs, Stage 2 to the stomach, and Stage 3 to the kidneys. At each stage, they suggested distinct treatment strategies for "Consumptive Thirsty" Syndrome (diabetes).

Utilizing the correlation between TCM and signaling molecules, we conducted an analysis of the TCM approach for treating diabetes at different stages from a molecular perspective. Our investigation revealed that TCM and modern medicine employ comparable strategies for treating diabetes.

Molecular basis of TCM treatments for Stage 1 Consumptive-Thirsty Syndrome (diabetes)

According to TCM, the first stage of "Consumptive-Thirsty" Syndrome (diabetes) is associated with the lungs due to its anatomical location at the upper part of the body. TCM terminology for this stage is "Upper Consumption." (12, 13)."Research on Recipes" is an ancient TCM book authored by Kun Wu during the Ming Dynasty (14). Volume 4 of this book includes a treatment method for Upper Consumption, which involves using a combination of Coptis chinensis powder, Trichosanthes root powder, human milk, and juice of lotus root. In physiological terms, the inhibitory effect of these four herbal medicines on FOXO1 is presented in Table 2 and illustrated in Figure 3.

The TCM strategy for treating Stage 1 "Consumptive-Thirsty" Syndrome involves inhibiting FoxO1. Since the expression of FoxO1 protein in the liver is crucial in promoting hepatic glucose production as well as being one of the factors that stimulate glucose synthesis within the liver (7), Coptis chinensis, which reduces FoxO1 in the liver and inhibits hepatic gluconeogenesis (15), supports the TCM strategy, which is in line with modern medicine.

Molecular basis of TCM treatment for Stage 2 Consumptive-Thirsty Syndrome (diabetes)

In the context of Stage 2 of "Consumptive-Thirsty" Syndrome (diabetes), TCM theory holds that it is associated with the stomach, which is situated in the middle location of the body and is referred to as "Middle Consumption" (12, 13). An ancient TCM book "Research on Recipes" (14), mentioned the use of "Tiaowei Chengqi Decoction (TCD)", which consists of Rhubarb, Mirabilitum and licorice, to address the symptoms of this stage. The prescription is indicated for patients with Middle Consumption

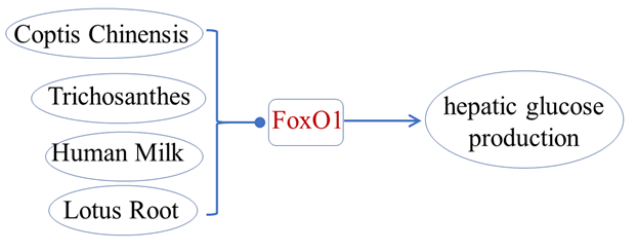

Figure 3. The effect of TCM herbal medicines on FoxO1. The arrow indicates increasing, and the solid circle indicates inhibiting effects.

Table 2. TCM formula to treat upper consumption.

Herbal medicine	Effects on FoxO1
Coptis chinensis	Berberine, a compound that can be extracted from different plant sources including Coptis chinensis, has been found to lower FoxO1 expression in the liver and inhibit hepatic gluconeogenesis. (15).
Trichosanthes	Trichosanthes pericarpimm inhibits FoxO1 (16).
Human milk	Milk signaling has been found to down-regulate the essential transcription factor FoxO1, which in turn results in the up-regulation of insulin promoter factor-1. This up-regulation stimulates β-cell proliferation, insulin secretion, and the co-expression of islet amyloid polypeptide. (17).
Lotus root	FoxO3 stimulates the expression of FoxO1 and FoxO4 (18). The administration of Lotus leaf has been found to significantly reduce the gene expression of FoxO3a. (19).

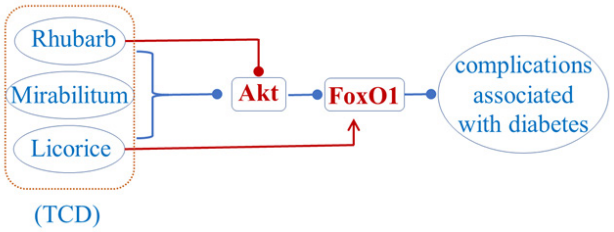

Figure 4. The effect of TCD on FoxO1. The arrow indicates increasing, and the solid circle indicates inhibiting effects.

who eat excessively and experience increased urination. The formula is said to effectively treat this condition.

In physiological processes, the PI3K/Akt pathway serves as the primary regulatory pathway for FoxO1 protein. Phosphorylation of FoxO1 by Akt leads to the inhibition of FoxO1's transcriptional activities (20). However, Tiaowei Chengqi Decoction (TCD, Rhubarb & Mirabilitum Combination) has been shown to significantly increase the phosphorylation of PI3K and Akt (21), which suggests that TCD may increase FoxO1 activity. Additionally, it should be noted that rhein, an anthraquinone compound found in the TCM rhubarb, functions as a natural agent that inhibits Akt (22). Furthermore, licorice flavonoid has been shown to activate FoxO1 (23). A detailed depiction of these interactions is presented in Figure 4.

Thus, the TCM approach to treating Stage 2 "Consumptive-Thirsty" Syndrome involves enhancing FoxO1. As the activation of FoxO1 in the kidney has the potential to prevent diabetes-associated complications (7, 9), the TCM approach aligns with that of modern medicine.

Molecular basis of TCM treatment for Stage 3 Consumptive-Thirsty Syndrome (diabetes)

In the third stage of "Consumptive-Thirsty" Syndrome, TCM attributes the condition to the kidneys as they are located in the lower region of the body, thus referred to as "Lower Consumption" (12, 13). The ancient TCM book, "Three Consumptions Theory" (12), lists various causes of "Consumptive-Thirsty" Syndrome, as shown in Table 3, and compares them to molecular mappings.

Hence, the pathological characteristics of "Consumptive-Thirsty" Syndrome in TCM are akin to those observed in diabetes under the purview of contemporary medicine. The ancient text, "Research on Recipes" (14), describes the composition of Liuwei Dihuang Pill as comprising Rehmannia, Cornus officinalis, Dioscorea polystachya (Yam), Poria, the bark of tree peony root, and Alismatis Rhizoma. The text further elucidates that the patients with lower Consumption, who exhibit symptoms of Polydipsia and cream urine, can be treated with this pill. In TCM,

Table 3. Causes of "Consumptive-Thirsty" Syndrome and their Molecular Mappings.

Cause of "Consumptive-Thirsty" Syndrome (12)	Molecular mappings
Yin Qi is extremely weak in the patient with "Consumptive-Thirsty" Syndrome. ** Yin Qi corresponds to Potassium (K).	Individuals with low potassium levels have been shown to secrete lower amounts of insulin, have elevated blood sugar levels, and are at an increased risk of developing type 2 diabetes, compared to those with normal potassium levels (24).
Yang Qi is very high in the patient with "Consumptive-Thirsty" Syndrome. ** Yang Qi corresponds to Calcium (Ca).	Throughout an average follow-up period of 8.8 years, 1516 cases of diabetes were reported, and an elevated level of serum calcium was found to be linked to an increased risk of type 2 diabetes. (25).
For patients with "Consumptive-Thirsty" Syndrome, their Genuine Qi becomes weak. If warm medicines are used to supplement the Genuine Qi, the patient's thirst stops, their urine returns to normal, and they recover from their illness. ** Genuine Qi corresponds to Phosphorus (P).	There is a substantial decrease in the serum level of phosphorus observed in patients with type 2 diabetes (26).
In patients diagnosed with the "Consumptive-Thirsty" syndrome, the Kidney Yin exhibits a state of coldness. The consumption of cold medicine exacerbates this condition, leading to a weakening of the Kidney Yin. Conversely, the administration of treatments that strengthen the Kidney Yin results in the cessation of thirst, normalization of urine output, and eventual recovery from the underlying illness. ** Kidney Yin corresponds to Wnt.	Type 2 diabetes is marked by insulin resistance, insufficient insulin production, and elevated blood glucose levels. The activation of Wnt activity is believed to hold promise as a potential form of treatment for type 2 diabetes (27).

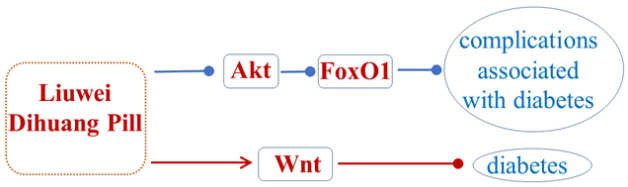

Figure 5. Effect of Liuwei Dihuang Pill on FoxO1. The arrow indicates increasing, and the solid circle indicates inhibiting effects.

Liuwei Dihuang Pill is renowned for its efficacy in nourishing Kidney Yin (Wnt) (3).

Physiologically, Liuwei Dihuang Pill has been shown to inhibit the expression of PI3k, mTOR, and Akt (28). Akt, in turn, phosphorylates FoxO1 and impedes its transcriptional functions, as evidenced in (20). Consequently, the inhibition of Akt would result in an increase in FoxO1. Furthermore, It was demonstrated that Liuwei Dihuang Pill could enhance the protein and gene expression of Wnt1, Wnt3a, and β-catenin, thereby activating the Wnt/β-catenin signaling pathway (29).

Studies have shown that the activation of FoxO1 in the kidney can help prevent complications linked to diabetes (7, 9). Moreover, enhancing Wnt activity has been suggested as a plausible approach for treating type 2 diabetes, as elucidated by (27). Therefore, the TCM approach to managing Stage 3 Consumptive-Thirsty Syndrome aligns with the therapeutic approach taken by modern medicine in managing diabetes. The details of this alignment are illustrated in Figure 5.

The influence of FoxO1 on Wnt, Calcium, Potassium, and Phosphorus is indeed intriguing. FoxO1 is known to enhance the expression of canonical Wnt genes (30). Calcium ions are crucial for cellular signaling within skeletal muscle. Excessive calcium in the sarcoplasm can induce muscle fiber atrophy and, in extreme cases, cell death. This accumulation can also lead to mitochondrial inactivation and a decrease in skeletal muscle function (31). FoxO proteins play a vital role in maintaining muscle strength as they regulate genes involved in calcium signaling. This discovery paves the way for further investigation into the mechanisms by which the insulin receptor (IR)/insulin-like growth factor 1 receptor (IGF1R) and FoxO pathways control calcium balance, especially in relation to muscle atrophy associated with diabetes (32). It is established that Akt phosphorylates FoxO1, thereby inhibiting its transcriptional functions (20), and that PI3K/Akt signaling reduces sarcolemmal potassium currents in neonatal rat cardiac myocytes (33). This suggests that a decrease in Akt would result in increased FoxO1 and potassium current, or that higher FoxO1 levels would correspond to increased potassium levels. Furthermore, hyperphosphatemia has been found to inhibit the Akt/mTOR signaling pathway (34), suggesting that a decrease in Akt would correspond to increased phosphate and FoxO1 levels. These effects of FoxO1 align with the principles of traditional Chinese medicine.

Furthermore, as outlined in Table 4, Liuwei Dihuang Pill or its constituent compounds have been shown to increase Potassium levels, suppress Calcium levels, and increase Phosphorus and Wnt activities. According to a study conducted in (35), the combination of Liuwei Dihuang Pill and losartan potassium has demonstrated a favorable clinical efficacy in treating early-stage diabetic nephropathy. This combination therapy has been found to improve renal function and effectively reduce urinary microprotein levels, thereby presenting a certain clinical value.

The Na^+-K^+-ATPase pump located in the cell membrane is primarily responsible for maintaining the proper distribution of potassium between the cells and extracellular fluid. Excessively enhanced activity of the pump may contribute to temporary hypokalemia as a result of an influx of potassium into cells, as reported by (36). However, experimental studies involving hyperthyroid rats have shown that Liuwei Dihuang Pill, a TCM remedy, can effectively reduce the activity of the Na^+-K^+-ATPase pump in liver tissue and thyroid hormone levels, leading to increased potassium levels.

According to (37), Rehmannia contains a higher amount of phosphorus. The concentration of calcium inside cells is significantly lower compared to that in the extracellular fluid. This considerable concentration gradient is preserved through limited permeability, calcium extrusion pumps, and highly efficient binding by intracellular stores (38). The major phenolic compound named Paeonol, which is obtained from the root bark of Paeonia moutan, has been discovered to escalate the concentration of intracellular calcium. This highlights that it may reduce the concentration of extracellular and plasma calcium (39). In addition, Paeonol was shown to block L-type calcium channel current (40). The primary subset of triterpenes found in Alismatis rhizoma is known as alisols (41), and it has been found that alisol-B administration significantly suppresses hypercalcemia (42).

Summary of TCM Strategies to Treat Diabetes

In TCM, the progression of diabetes, or "Consumptive Thirsty" Syndrome, is classified into three stages, each with different treatment approaches. TCM views the primary factor in this syndrome as "Consumption" (referring to FoxO1), and the focus of treatment is to regulate this factor.

Figure 6 illustrates a comparison of the perspectives on diabetes between TCM and modern medicine. TCM posits that the "Consumptive-Thirsty" Syndrome in Stage 1 is associated with the lung (12, 13). In a physiological context, patients with mild asthma display significantly elevated levels of the FoxO1 gene in their airway macrophages (43), and FoxO1 is involved in muscle cell dege-

Table 4. Effect of herbal medicine on Ca, K, P and Wnt.

TCM medicine	Effects on Ca, K, P, Wnt
Liuwei Dihuang Pill (29, 36)	K ↑, Wnt ↑
Rehmannia (37)	P ↑
bark of tree peony root (39, 40)	Ca ↓
Alismatis rhizome (42)	Ca ↓

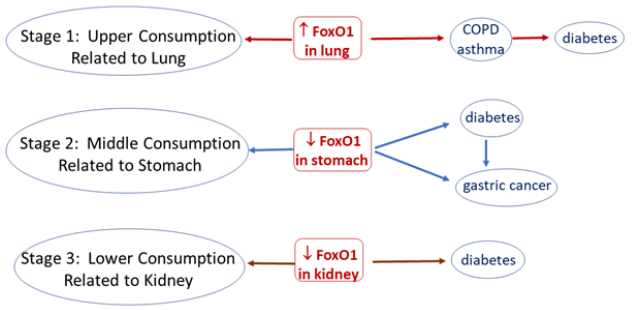

Figure 6. Comparison of views on diabetes between TCM and modern medicine.

neration in individuals experiencing chronic obstructive pulmonary disease (COPD) (44). Furthermore, diabetes mellitus is a frequent comorbidity that occurs concurrently with the diagnosis of COPD. It's also fairly common for patients with COPD to develop diabetes mellitus as their condition progresses (45). The TCM treatment for Stage 1 entails the inhibition of FoxO1, which aligns with modern medical practice.

In Stage 2, the "Consumptive-Thirsty" Syndrome is linked to the stomach according to TCM (12, 13). From a physiological perspective, a decrease in the levels of FoxO1 significantly boosts the proliferation of gastric cancer cells, while FoxO1 functions as a tumor suppressor in relation to gastric cancer (46). Furthermore, individuals with diabetes are at a higher risk of developing gastric cancer (47). The TCM treatment for the Middle Consumption stage involves increasing FoxO1 levels, which aligns with modern medical practice.

In Stage 3, the "Consumptive-Thirsty" Syndrome is associated with the kidney in TCM (12, 13). Physiologically, the expression of FoxO1 is reduced in kidney cells of diabetic mice both in vitro and in vivo when exposed to high levels of glucose. Diabetes may have an impact on FoxO1 within the nucleus and cytosol of cells. An increase in glucose concentration in kidney cells can also stimulate the activation of the Akt cascade, leading to a rise in the degradation of FoxO1 (7, 9). FoxO1 plays a protective role in kidney tissue (7, 10). The TCM treatment for the Lower Consumption stage involves increasing FoxO1 levels, which aligns with modern medical practice.

The Implications of TCM Strategies for Diabetes Treatment in Modern Medicine

The TCM approach to diabetes treatment involves enhancing the expression of FoxO1 and increasing the levels of potassium, phosphorus, and Wnt, while simultaneously decreasing calcium concentrations. The methods to achieve these objectives are well-established in contemporary medicine.

FoxO transcription factors are central regulators of cellular homeostasis. FoxOs respond to a wide range of external stimuli, including growth factor signaling, oxidative stress, genotoxic stress, and nutrient deprivation. These signaling inputs regulate FoxOs through a number of post-translational modifications, including phosphorylation, acetylation, ubiquitination, and methylation (48). FoxO activity, stability, and localization can be regulated by the insulin/insulin-like growth factor (IGF) signaling pathway and reactive oxygen species (ROS). Insulin/IGF activates transmembrane receptors and in turn, activates the insulin receptor substrate (IRS) proteins. These IRS proteins then trigger a series of downstream signaling events, culminating in the phosphorylation and activation of AKT. Once activated, AKT phosphorylates FoxO proteins. Contrary to the inhibitory effect of insulin/IGF signaling, reactive oxygen species (ROS) encourage the nuclear localization and activation of FoxOs. Upon activation, FoxOs regulate several cellular processes that promote cellular homeostasis (48). Furthermore, FoxO1 is activated in response to bacterial or cytokine stimulation. Its translocation to the nucleus and subsequent binding to promoter regions of genes containing FoxO response elements are facilitated by the MAP kinase pathway while being inhibited by the PI3K/Akt pathway. The downstream gene targets of FoxO1 include pro-inflammatory signaling molecules such as TLR2, TLR4, IL-1β, and TNF-α. (49).The body needs potassium for almost everything it does, including proper kidney and heart function, muscle contraction, and nerve transmission. Potassium is an essential element found in many foods, including fruits such as dried apricots, prunes, raisins, orange juice, and bananas; vegetables such as acorn squash, potatoes, spinach, tomatoes, and broccoli; lentils, kidney beans, soybeans, and nuts; milk and yogurt; meats, poultry, and fish. Potassium is also contained in many multivitamin/multimineral supplements and in supplements that contain only potassium. Potassium in supplements comes in many different forms - a common form is potassium chloride, but other forms used in supplements are potassium citrate, potassium phosphate, potassium aspartate, potassium bicarbonate, and potassium gluconate (50).

Phosphorus is a component of bones, teeth, DNA, and RNA. In the form of phospholipids, phosphorus is also a component of cell membrane structure and ATP. Phosphorus plays key roles in regulation of gene transcription, activation of enzymes, maintenance of normal pH in extracellular fluid, and intracellular energy storage. Many different types of foods contain phosphorus, including dairy products, meats and poultry, fish, eggs, nuts, legumes, vegetables, and grains (51). Phosphorus and calcium are interrelated because hormones, such as vitamin D and parathyroid hormone (PTH), regulate the metabolism of both minerals. The combination of high phosphorus intakes with low calcium intakes increases serum PTH levels. Moreover, a high phosphorus intake without adequate calcium intake seems to have negative impact on calcium metabolism (51, 52).

The Wnt protein family, known for its role in cellular processes such as development, stem cell preservation, and tissue regeneration, primarily triggers two intracellular signaling pathways. The canonical Wnt pathway utilizes β-catenin as the principal effector, transmitting signals to the nucleus and initiating the transcription of Wnt-specific genes that govern cell fate decisions across various cells and tissues. The second Wnt signaling pathway operates independently of β-catenin's signaling function (53). Wnt signaling can be stimulated through various approaches. These include the initiation of Wnt signaling via Wnt proteins and their mimics, the enhancement of Wnt signaling by inhibiting its suppressors, and the promotion of Wnt signaling by preventing the degradation of β-catenin (54).

Several well-established medications are available for the treatment of hypercalcemia. For instance, Calcito-

nin, a hormone derived from salmon, is used to regulate blood calcium levels. Calcimimetics are drugs designed to manage overactive parathyroid glands. Additionally, Bisphosphonates, a class of intravenous osteoporosis drugs, can rapidly reduce calcium levels (55). Moreover, pharmacotherapies based on Calcitonin have been developed for the treatment of diabetes-related conditions (56).

Conclusion

Traditional Chinese medicine views diabetes as the "Consumptive-Thirst" syndrome and emphasizes the importance of the FoxO1 molecule in the disease process. TCM categorizes this syndrome into three distinct stages, each with its own unique treatment approach. In the first stage, TCM aims to inhibit FoxO1, aligning with the initial treatment strategy of contemporary medicine. However, in the later stages of the disease, TCM suggests increasing FoxO1 expression, which is also supported by modern medicine. In the third stage, TCM utilizes the well-known herbal formula Liuwei Dihuang Pill to enhance the expression of FoxO1, potassium, phosphorus, and Wnt, while reducing calcium levels. Understanding the molecular mechanisms behind TCM's diabetes theory will offer new therapeutic avenues for treating the disease.

Interest conflict

The authors declare no conflict of interest.

Consent for publications

The authors have read and proved the final manuscript for publication.

Availability of data and material

All data generated during this study are included in this published article.

Authors' Contribution

All authors have equal roles in study design, work, statistical analysis and manuscript writing.

Funding

This work is supported by the Key Research and Development Projects of Sichuan Province (2023YFS0075) awarded to Ye Zeng.

Ethics approval and consent to participate

No human or animals were used in the present research.

References

1. Li X, Liu H, Feng H, Xian Z, Chen Y, Chen J, Tang C, Lai X, Lan X, Huang H, et al. Acupuncture paired with herbal medicine for prediabetes: study protocol for a randomized controlled trial. Trials 2017; 18:297.
2. Gomperts BD, Gomberg ESL, Bastien DG, Tatham PE. Signal transduction. Gulf Professional Publishing, 2002.
3. Liu Y. The Mapping between Traditional Chinese Medicine and Signaling Molecules. Newcastle upon Tyne, UK: Cambridge Scholars Publishing, 2022.
4. Nakae J, Kitamura T, Kitamura Y, Biggs III WH, Arden KC, Accili D. The forkhead transcription factor Foxo1 regulates adipocyte differentiation. Dev Cell 2003; 4:119-29.
5. Sinaiko AR, Caprio S. Insulin resistance. The Journal of pediatrics 2012; 161:11-5.
6. InSug O, Zhang W, Wasserman DH, Liew CW, Liu J, Paik J, DePinho RA, Stolz DB, Kahn CR, Schwartz MW. FoxO1 integrates direct and indirect effects of insulin on hepatic glucose production and glucose utilization. Nature communications 2015; 6:1-15.
7. Benchoula K, Arya A, Parhar IS, Hwa WE. FoxO1 signaling as a therapeutic target for type 2 diabetes and obesity. Eur J Pharmacol 2020:173758.
8. Furuyama T, Kitayama K, Yamashita H, Mori N. Forkhead transcription factor FOXO1 (FKHR)-dependent induction of PDK4 gene expression in skeletal muscle during energy deprivation. Biochemical Journal 2003; 375:365-71.
9. Fiorentino L, Cavalera M, Menini S, Marchetti V, Mavilio M, Fabrizi M, Conserva F, Casagrande V, Menghini R, Pontrelli P. Loss of TIMP3 underlies diabetic nephropathy via FoxO1/STAT1 interplay. EMBO molecular medicine 2013; 5:441-55.
10. Qin G, Zhou Y, Guo F, Ren L, Wu L, Zhang Y, Ma X, Wang Q. Overexpression of the FoxO1 ameliorates mesangial cell dysfunction in male diabetic rats. Molecular Endocrinology 2015; 29:1080-91.
11. Sajan MP, Ivey RA, Lee MC, Farese RV. Hepatic insulin resistance in ob/ob mice involves increases in ceramide, aPKC activity, and selective impairment of Akt-dependent FoxO1 phosphorylation. Journal of lipid research 2015; 56:70-80.
12. Liu W. Three Consumptions Theory. Chinese Text Project 2021.
13. Zhu Z. Danxi's Mastery of Medicine Chinese Text Project, 1347.
14. Wu K. Research on Recipes. https://ctext.org/zh, 1586.
15. Xia X, Yan J, Shen Y, Tang K, Yin J, Zhang Y, Yang D, Liang H, Ye J, Weng J. Berberine improves glucose metabolism in diabetic rats by inhibition of hepatic gluconeogenesis. PLoS one 2011; 6:e16556.
16. Wang S. Hypoglycemic effect of Trichosanthes pericarpimm based on regulating intestinal microbiota in type 2 diabetic mice. Hefei University of Technology, 2020.
17. Melnik BC. Milk signalling in the pathogenesis of type 2 diabetes. Medical Hypotheses 2011; 76:553-9.
18. Essaghir A, Dif N, Marbehant CY, Coffer PJ, Demoulin J-B. The transcription of FOXO genes is stimulated by FOXO3 and repressed by growth factors. Journal of Biological Chemistry 2009; 284:10334-42.
19. Park SH, Oh J, Jo M, Kim JK, Kim DS, Kim HG, Yoon K, Yang Y, Geum J-h, Kim J-E. Water extract of Lotus leaf alleviates dexamethasone-induced muscle atrophy via regulating protein metabolism-related pathways in mice. Molecules 2020; 25:4592.
20. Nozhat Z, Mohammadi-Yeganeh S, Azizi F, Zarkesh M, Hedayati M. Effects of metformin on the PI3K/AKT/FOXO1 pathway in anaplastic thyroid Cancer cell lines. DARU Journal of Pharmaceutical Sciences 2018; 26:93-103.
21. Meng X, Ma J, Kang SY, Jung HW, Park Y-K. Jowiseungki decoction affects diabetic nephropathy in mice through renal injury inhibition as evidenced by network pharmacology and gut microbiota analyses. Chinese medicine 2020; 15:1-19.
22. Wang J, Liu S, Yin Y, Li M, Wang B, Yang L, Jiang Y. FOXO3-mediated up-regulation of Bim contributes to rhein-induced cancer cell apoptosis. Apoptosis 2015; 20:399-409.
23. Ruan S, Xiang S, Wu W, Cao S, Du Q, Wang Z, Chen T, Shen Q, Liu L, Chen H. Potential role of mTORC1 and the PI3K-Akt pathway in anti-acne properties of licorice flavonoids. Journal of Functional Foods 2020; 70:103968.
24. Watson S. The Link Between Diabetes and Potassium. WebMD, 2020.
25. Rooney MR, Pankow JS, Sibley SD, Selvin E, Reis JP, Michos ED, Lutsey PL. Serum calcium and incident type 2 diabetes: the Atherosclerosis Risk in Communities (ARIC) study. The Ameri-

can journal of clinical nutrition 2016; 104:1023-9.
26. Fang L, Li X. Level of serum phosphorus and adult type 2 diabetes mellitus. Zhong nan da xue xue bao Yi xue ban= Journal of Central South University Medical Sciences 2016; 41:502-6.
27. Bordonaro M. Role of Wnt signaling in the development of type 2 diabetes. Vitamins & Hormones 2009; 80:563-81.
28. Tao P. The Study of Liuwei Dihuang Pill on Prevent and Treating Diabetic Nephropathy Through PI3k/mTOR/AKt Signaling Pathway. Shanghai University of Traditional Chinese Medicine, 2019.
29. Chen P. Probe into Connotation of Interdependence between Storing and Discharging of Liver and Kidney Based on Proliferation and Differentiation of Neural Stem Cells in Vitro. Guangzhou University of Chinese Medicine, 2014.
30. Pintor S, Lopez A, Flores D, Lozoya B, Soti B, Pokhrel R, Negrete J, Persans MW, Gilkerson R, Gunn B. FOXO1 promotes the expression of canonical WNT target genes in examined basal-like breast and glioblastoma multiforme cancer cells. FEBS Open Bio 2023.
31. Nemirovskaya TL, Sharlo KA. Roles of ATP and SERCA in the regulation of calcium turnover in unloaded skeletal muscles: current view and future directions. International Journal of Molecular Sciences 2022; 23:6937.
32. Bhardwaj G, Penniman CM, Klaus K, Weatherford ET, Pan H, Dreyfuss JM, Nair KS, Kahn CR, O'Neill BT. Transcriptomic regulation of muscle mitochondria and calcium signaling by Insulin/IGF-1 receptors depends on FoxO transcription factors. Frontiers in physiology 2022; 12:2536.
33. Millis RM, Alvin ZV, Zhao A, Haddad GE. Effects of IGF-1 on and Channels via PI3K/Akt Signaling in Neonatal Cardiac Myocytes. International Journal of Cell Biology 2012; 2012.
34. Hsu Y-J, Hsu S-C, Huang S-M, Lee H-S, Lin S-H, Tsai C-S, Shih C-C, Lin C-Y. Hyperphosphatemia induces protective autophagy in endothelial cells through the inhibition of Akt/mTOR signaling. J Vasc Surg 2015; 62:210-21. e2.
35. Wang J. Clinical study on Liuwei Dihuang Pills combined with losartan potassium in treatment of early diabetic nephropathy. Drugs and Clinic 2015; 30:674-7.
36. Mount DB. Causes of hypokalemia in adults. UpToDate, Waltham, MA(Accessed on August 5, 2016) 2016.
37. Du H, Zhao X, Liu G, Liu F. Quality of dihuang (Rehmannia spp.). Zhongguo Zhong yao za zhi= Zhongguo Zhongyao Zazhi= China Journal of Chinese Materia Medica 1992; 17:327-9, 81.
38. Atchison DK, Beierwaltes WH. The influence of extracellular and intracellular calcium on the secretion of renin. Pflügers Archiv-European Journal of Physiology 2013; 465:59-69.
39. Li M, Tan SY, Zhang J, You HX. Effects of paeonol on intracellular calcium concentration and expression of RUNX3 in LoVo human colon cancer cells. Molecular Medicine Reports 2013; 7:1425-30.
40. Zhang G, Hao X, Zhou P, Wu C. Effect of paconol on L-type calcium channel in rat ventricular myocytes. Methods and findings in experimental and clinical pharmacology 2003; 25:281-6.
41. Bailly C. Pharmacological Properties and Molecular Targets of Alisol Triterpenoids from Alismatis Rhizoma. Biomedicines 2022; 10:1945-64.
42. Lee J-W, Kobayashi Y, Nakamichi Y, Udagawa N, Takahashi N, Im N-K, Seo H-J, Jeon WB, Yonezawa T, Cha B-Y. Alisol-B, a novel phyto-steroid, suppresses the RANKL-induced osteoclast formation and prevents bone loss in mice. Biochemical Pharmacology 2010; 80:352-61.
43. Chung S, Kim JY, Song MA, Park GY, Lee YG, Karpurapu M, Englert JA, Ballinger MN, Pabla N, Chung HY. FoxO1 is a critical regulator of M2-like macrophage activation in allergic asthma. Allergy 2019; 74:535-48.
44. Pomiès P, Blaquière M, Maury J, Mercier J, Gouzi F, Hayot M. Involvement of the FoxO1/MuRF1/Atrogin-1 signaling pathway in the oxidative stress-induced atrophy of cultured chronic obstructive pulmonary disease myotubes. PLoS One 2016; 11:e0160092.
45. Ho T-W, Huang C-T, Ruan S-Y, Tsai Y-J, Lai F, Yu C-J. Diabetes mellitus in patients with chronic obstructive pulmonary disease-The impact on mortality. PLoS One 2017; 12:e0175794.
46. Shi F, Li T, Liu Z, Qu K, Shi C, Li Y, Qin Q, Cheng L, Jin X, Yu T. FOXO1: Another avenue for treating digestive malignancy? Seminars in cancer biology: Elsevier, 2018:124-31.
47. Tseng C-H, Tseng F-H. Diabetes and gastric cancer: the potential links. World journal of gastroenterology: WJG 2014; 20:1701.
48. Brown AK, Webb AE. Regulation of FOXO factors in mammalian cells. Current topics in developmental biology 2018; 127:165-92.
49. Graves DT, Milovanova TN. Mucosal immunity and the FOXO1 transcription factors. Frontiers in immunology 2019; 10:2530.
50. Supplements OoD. Potassium. National Institutes of Health (NIH) 2021.
51. Supplements OoD. Phosphorus. National Institutes of Health, 2023.
52. Trautvetter U, Jahreis G, Kiehntopf M, Glei M. Consequences of a high phosphorus intake on mineral metabolism and bone remodeling in dependence of calcium intake in healthy subjects–a randomized placebo-controlled human intervention study. Nutrition journal 2015; 15:1-11.
53. Valenta T, Hausmann G, Basler K. The many faces and functions of β-catenin. The EMBO journal 2012; 31:2714-36.
54. Bonnet C, Brahmbhatt A, Deng SX, Zheng JJ. Wnt signaling activation: Targets and therapeutic opportunities for stem cell therapy and regenerative medicine. RSC chemical biology 2021; 2:1144-57.
55. Clinic M. Hypercalcemia. MAYO Clinic, 2021.
56. Mathiesen DS, Lund A, Vilsbøll T, Knop FK, Bagger JI. Amylin and calcitonin: potential therapeutic strategies to reduce body weight and liver fat. Frontiers in Endocrinology 2021:1016.