A Framework for T2D Management & Knowledge Discovery of Complications in the Context of Chinese Culture: From Triggers to Causalities

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Keywords: Type II Diabetes Management, Symptoms, Patterns, Complications, Correlations, Knowledge Discovery.

Abstract: **Background:** With the ever-increasing number of Type-2 Diabetes (T2D) patients and its mortality rate in China, the medical care system is under huge pressure with all other related complications in the world's largest population. Failing to afford the needed resources on T2D management after patients leaving the hospital, the burden and challenges of diabatic complications have become more acute than ever. In the context of the Chinese culture, especially the habits and priority of eating in the daily life makes it even harder for T2D patients to control and manage. Limited knowledge of complications and their causalities are the biggest challenges faced by doctors all around the world. Only with the knowledge on the progression and evolution of T2D and its complications can doctors have the opportunity to find solutions. To tackle this daunting challenge, a system is in urgent need that can collect the real-time, patient-generated data which will unveil the patterns about the triggers and causalities for better decision-making and, in the long run, provide an overarching understanding of the progression and evolution of T2D and its complications.

Methods: To systematically place the data in the hands of patients, knowledge discovery based on data mining for the proposed framework can be of very high feasibility and accuracy. The triggers, anomalies in patients' daily life, remind patients to provide the related data input for the analysis of the risk factors, patterns, and causalities of complications in the progression of T2D. Behind the triggers, the related known symptoms correlated with the internal organs, are classified by their severity and locations in bodies. Distant-aid like first responders will be arranged if very high-risk factors occur. Auto responses of suggestions will be given to patients if the condition is not urgent. The discovered patterns and causalities will be stored in the knowledge pool for future research and medicine development.

Results:

1. The associations between and among the internal organs brought about by the patterns behind the triggers under urgent and non-urgent situations will give us answers to the current puzzles of the end-stage complications.
2. Supported by the updates of patient-provided data on the anomalies going on in their bodies, the data mining output of the correlation between internal organs and different complications can be of high accuracy with the "1 to 1", "1 to n" and "n to 1" relationships between symptoms and organs, organs and organs.
3. The collected symptoms correlating to the pathological changes of each individual internal organ can reshape our understanding about the functions of their own and as a part of the whole system of the human body.
4. The patterns of the known and newly discovered complications and their causalities will help doctors gain an overarching understanding of the progression and evolution of T2D and its complications.
5. The discovered knowledge will help doctors anticipate the upcoming progressions of diseases at an expert level with the level of comprehension well beyond the individual physician's practice experience.

Conclusions: With the application of this framework to the management of T2D and other chronic diseases for different groups of users, its knowledge pool will be continually enriched and enlarged. Its scalability on diseases and causalities will probably change many current definitions and enlarge the boundary of medical science.

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1 INTRODUCTION

Type-2 Diabetes (T2D) and its ineffective management have been challenging the health of a very large population in China. By the figures given in the IDF Diabetes Atlas Ninth edition 2019, approximately 463 million adults (20-79 years) had been living with diabetes; by 2045 this will rise to 700 million. According to the most recent study of the prevalence of T2D in mainland China, by the standard of HbA1c ≥6.5%, the average percentage of diagnosed and premature T2D has reached 12.8%, which means almost half of the adult population suffer from the dysfunction of the glucoregulatory system with a fast-growing tendency after age 50. (Li, et al., 2020) The total number of people with T2D has reached about 1.164 million in China, the largest in the world. The percentage of diabetes among people above 60 has reached more than 20% by 2016. (Yang, Lu, Weng, et al. 2010) With the obesity rate for adults over 18 already at 11.9% in 2015, the harm of hyperglycemia goes on before the premature stage till the occurrence of all kinds of end-stage complications related to cardiovascular diseases, microangiopathy, cancer, stroke, Alzheimer's disease, and depression. (Report on nutrition and chronic diseases of the Chinese population 2015, Chinese Medical Association, Diabetes Branch 2018) Proportion of microalbuminuriax, macroalbuminuria, and renal failure in patients with T2D nephropathy has reached 25.26%, 4.34%, and 7.03% respectively. 14.9% of the patients suffer from retinopathy while 24.05% have diabetic peripheral neuropathy. (ADA 2019) 10.56% of all patients who went through peripheral artery disease tests (PAD tests) such as Ankle-Brachial Index (ABI), angiograms, ultrasound, or MRI got diagnosed with peripheral artery disease. (ADA 2019) Out of 33.9% of patients with cardiovascular disease, 94.9% put up with atherosclerotic cardiovascular disease (ASCVD). (Hong, Mosenzon, Alguwaihes, Arenas Leon, et al. 2020) All these problems pose a huge burden to the health system and great risks to the wellbeing of T2D patients.

T2D management is the crucial part of the whole course of prevention, intervention and treatment of complications rather than just screening for the end-stage ones. At present, insulin administration is the main treatment for T2D patients, when hyperglycemia cannot be controlled through diet, exercise, and oral medication. (Kavakiotis, Ioannis, Tsave, Olga, Salifoglou, Athanasios, Maglaveras, Nicos, Vlahavas, Ioannis, Chouvarda, Ioanna 2017) But according to Research Report on Burden of Injection and Administration of Diabetic Patients, 90% of patients around the world who administer daily injections think this therapy is impacting their normal way of life; 72% think the inconvenience of injection has a negative effect on following doctor's orders; 32%

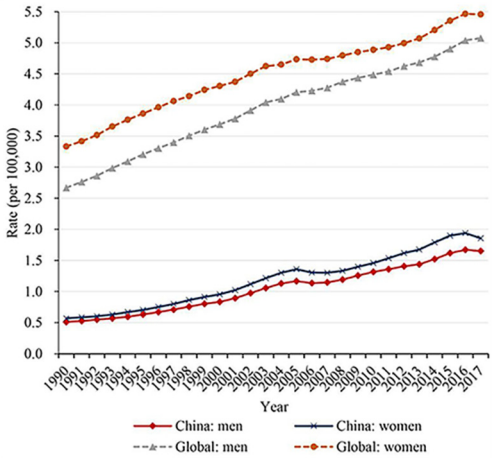

Figure 1: Prevalence of diabetes in China and around the world from 1990 to 2017. Credit: Xiaoxue L, Chuanhua Y, et.al. *Trends in the Incidence and Mortality of Diabetes in China from 1990 to 2017: A Joinpoint and Age-Period-Cohort Analysis*. CMR: crude mortality rate; ASMR: age-standardized mortality rate.

gave up injection therapy because of the inconvenience. (IQVIAA *Study of the Burden of Administration Modalities in Patients with Injectable Hypoglycemia*.) Similar problems exist among T2D patients in China. According to a one-year cohort study by He, et.al., the mean medicine preservation rate (MPR) of T2D patients only reached 0.499 with 14.1% and 29% of discontinuations in the first month and the first three months respectively. Only 53% of the patients remain persistent, where the average time to non-persistence in the study was 230.3 days. (Zhao, et al. 2019) Apart from that, data from a survey by Liu Xiaoxue, et.al. show that 39.1% of the respondents reported experiencing at least one insulin injection-related needle-stick injuries (NSIs) and 3.2% reported HBV infections while 0.9% had HCV infection as a result of NSIs. (Liu, et al. 2020) As a result, the prevalence of complications and mortality have always been on the rise in China as shown in figure 2 and 3. (Nam, et al. 2011, Ma, Ronald 2018, Lee, Keen, Bennett, Fuller, Lu 2001)).

Studies on the complications caused by T2D have been few and information on their causalities is very limited. This is mostly due to the absence of symptom-based triggers or alarms for both patients and doctors to get actively involved in generating data and feedback. (Chaki, Jyotismita, et al. 2020) Even

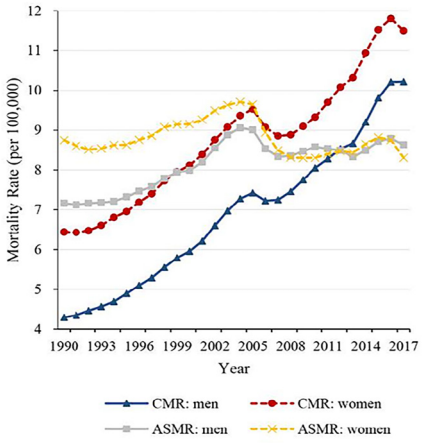

Figure 2: The mortality rate of diabetes classified by sex groups from 1990 to 2017. Credit: Xiaoxue L, Chuanhua Y, et.al. *Trends in the Incidence and Mortality of Diabetes in China from 1990 to 2017: A Joinpoint and Age-Period-Cohort Analysis.* CMR: crude mortality rate; ASMR: age-standardized mortality rate.

with machine learning and artificial intelligence applied in various products, most of them have not led to practical solutions for real-world problems. (Yao, Grace, et al. 2002) Without data to trace down the correlation between T2D and internal organ's deterioration and dysfunction going on in the course of diabatic progression and evolution, it is hard for doctors to make decisions or provide the needed intervention and treatment in time. Individualized plans and services are for sure out of the question. Therefore, this paper aims to propose a conceptual framework using the anomalies in patients' daily life in correlation with the internal organs as triggers to collect the patient-generated data in order to discover patterns in the progression and the evolution of T2D and its complications and form an overarching understanding of the causalities in the context of the Chinese culture.

2 THE CULTURAL CONTEXT OF T2D MANAGEMENT IN CHINA

In western countries, over 75% of individuals diagnosed with T2D receive exclusive care from primary care providers. Yet, only about one-third of patients correctly follow the health care provider's directions for T2D management. (Gao, et al. 2017) In China, doctors do a very good job educating patients for glucose monitoring and control, food intake, and the need for regular exercises while they are in the hospital for deciding their dose of insulin injections or hypoglycemic agents. It all depends on the patients to manage and take care of themselves once they leave the hospital. When it comes to complications, doctors have little clue about what has caused them or how they have developed. What's more, in the current health care system in China with the increasing numbers of patients and types of diseases, overstretched doctors can spare at most 5 to 10-min for each office visit. For patients, it is a headache just to think about the large crowds, long lines, and

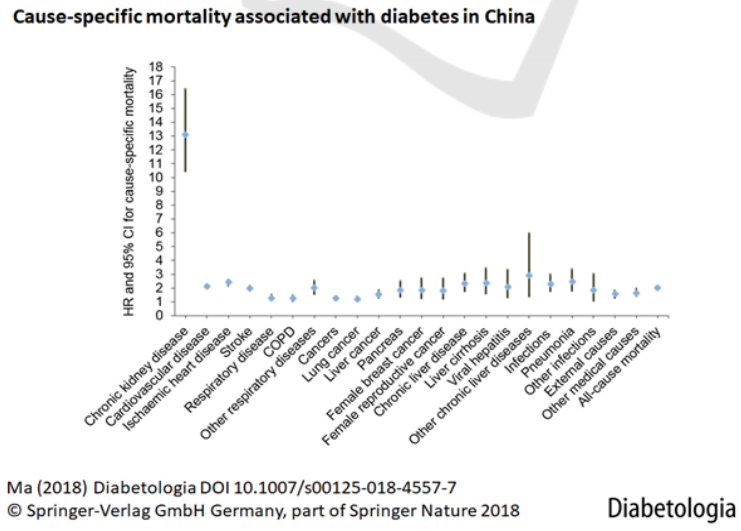

Figure 3: Cause-specific mortality rate associated with diabetes complications in China. Figure credit: Ronald C, W. Ma, *Epidemiology of diabetes and diabetic complications in China*. Diabetologia 61.6 (2018): 1249-1260. Data credit: Lee ET, Keen H, Bennett PH, Fuller JH, Lu M (2001) *Follow-up of the WHO Multinational Study of Vascular Disease in Diabetes: general description and morbidity*. Diabetologia 44(Suppl 2): S3–S13.

prescription. It is also expensive to stay in the hospital for the needed adjustments or the change of medications. For convenience, patients tend to be easily convinced by the salespersons in pharmacies for the promoted OTC medicines. The huge market potential has brought about the fierce competition for users among T2D management applications and platforms implemented with machine learning and AI. Unfortunately, most of the products have been unsuccessful and costly for the mere responses on the collected data of the glucose, blood pressure, daily exercises rather than the real-time conditions that T2D patients suffer from in their daily life. (Wasserman, Jason Adam, and Brian Philip Hinote 2011).

T2D and its complications, being endemic, have other cultural factors to be considered in the management, which include food and dietary preference, lifestyles, and beliefs about general health. (Shumaker, Schron, Ockene, McBee 2004, Diabetes Reduces the Rate of Sputum Culture Conversion in Patients with Newly Diagnosed Multidrug-Resistant Tuberculosis) In Chinese culture, the freedom to enjoy food plays a critical role in one's quality of life. (Nam, et al. 2011) Thus, the food culture in China creates all kinds of barriers and numerous problems for T2D patients, making it unbelievably hard for them to handle their management. Together with the general belief about health in the Chinese society that patients with chronic medical problems gradually become experts themselves, T2D management in China is a tough war against the limited healthcare resources, the natural instinct, social pressure, eating habits and preference, and the confusing information in this age of self-media.

When we look into the food structure in China, though the proportion of protein and vegetables has been growing, the intake of carbohydrates has stayed inordinate. People throughout the country start their day with dumplings, deep-fried dough sticks, noodles, porridge, and pancakes. Lunch is always built upon rice or noodles. And dinner consists of steamed bread, dumplings or pancake with porridge and a few dishes of vegetables or pickles. What's more, most people feel that they are never full without a bowl of rice or noodles no matter how many dishes they have eaten at a meal. The increasing number of dishes on the Chinese dining tables means a significant increase in the total amount of vegetable oil, animal fat, sugar, and salt. Though the awareness of a healthy life has been increasing among the whole population, the busy life leaves little time for regular physical exercises, which is another reason for the increasing numbers of hyperlipidemia, hyperglycemia, hypertension, and obesity in this country.

Eating in China is forever the highest priority in everyday life. Eating well is considered as the most basic enjoyment, freedom, and the meaning of life. Varieties on the daily menu are a must for every family, and feasts at weekends and festivals have been a routine. Meals for social purposes are hard to turn down. The normality on these occasions is to include as many good dishes as possible and the hosts/hostesses will try their best to push people to try everything on the table to show their hospitality. Wine and liquor are proposed and taken as signs of respect and gratitude to others. More will be poured if one takes up and finishes the glass even if the person is not good at drinking or has stated the medical or other reasons. T2D patients have to face, involve and interact with others on such occasions, where it is socially unacceptable to refuse and impossible for them to resist the good food or to follow the strict limitations on food intake. And the thought of just trying a little of each dish often results in the intake of food out of the right order with carbohydrates and energy considerably exceeding the right amount for T2D patients.

Also, the confusing and misleading information from the internet and peer experience make T2D management even harder. With the general belief of health in China, it is not hard to assume how much more T2D patients fail to correctly follow the health care provider's directions than the two-thirds out of 75% of patients in western countries. (Jason Fung) Many patients tend to trust their perception when they change their medications with over-the-counter medicines without asking doctors for their advice until they encounter serious troubles. To manage T2D at the national level, the guidelines in the Treatment and Prevention Guide for Type 2 Diabetes in China (version 2017) on the homepage of China CDC give clear directions: 1) collecting data about the patients' condition, knowledge, behaviors, and psychology; 2) pinning down the problems; 3) making plans for management and treatment; 4) providing the planned individual service; 5) giving feedback for adjusting the plan. To put these jobs down to earth, we need to pin down the triggers, find patterns supported with valid data about the causalities and evolutions of all diabetic complications.

3 TRIGGER ANALYSIS FOR T2D MANAGEMENT

In the context of this culture, it is obvious that most of the diseases and anomalies are the consequences of the unregulated food structure and intake. There are too many variables to consider if we require patients to provide the details of their daily meals. And it is really hard to give the right directions on what and how much exercise to take without the information of patients' current physical conditions. In the course of insulin injection treatment and T2D management, patients tend to be numb about the physical anomalies as long as they see that their glucose level is under check. It is exactly these physical discomforts and anomalies that build up the complications. Just like other diseases, only when people feel the physical discomfort, pain or anomalies, can they be alarmed to ponder about the reasons or whether they should go to the hospital. Thus, to collect such patient-generated data on their daily problems for the knowledge discovery about the evolution of the T2D complications, the symptoms that can alarm the patients and push them to turn for help should also be recorded and used as triggers apart from the most recent records of the glucose level and blood pressure.

Thirst

Diabetic thirst, or diabetes polydipsia, is caused by hyperglycemia which exhausts the kidneys in producing an excessive amount of urine and dehydrates the patients. The odds ratio of having the symptom of abnormal thirst is 1.37 times higher (1.17 to the power of 2) for someone with an FPG=11 mmol/L than for someone with an FPG=9 mmol/L (all other covariates being the same). (Drivsholm, de Fine Olivarius, Nielsen, & Siersma, 2005) Long-term polyuria can cause nausea, dizziness, headaches, fainting, and eventually uremia.

Urine problems

As the consequences of food, water, and drinks, urine problems are directly related to the functionalities of the bladder and kidneys. Patients with T2D, often suffer from pain and burning before, during, and after urination; passing only a small amount of urine after strong urges; trouble starting, and a weak stream of urine. Apart from these uncomfortable feelings, their urine is often with bubbles and a strong stench. For female patients, T2D independently increases the risk of urinary incontinence. (Lifford, Karen, et al. 2005)

Hard stool and diarrhea

With the progression of T2D, many patients often suffer from hard stools - as hard as pebbles sometimes. This is not just a sign of constipation, or only related to the bowels. The hard stool is the outcome of a combination of factors such as dry or inflamed digestive tracts. Apart from persistent hyperglycemia and the history of having T2D as the factors for diarrhea, cold and unsanitary food intake are also a strong trigger in China. In diabetic patients, metformin is a common cause of diarrhea. (Gould, Milena, and Joseph H. Sellin 2009) Diabetic patients are more likely to have associated diseases (e.g., celiac sprue and microscopic colitis) that present with diarrhea as the sole complaint. (Gould, Milena, and Joseph H. Sellin 2009) Ingested sugar-free foods that may contain sorbitol or other agents can cause diarrhea in T2D patients. Finally, diabetic enteropathy can itself cause diarrhea. (Gould, Milena, and Joseph H. Sellin 2009) Chronic diarrhea can bring about further complications.

Sputum

Diabetes is a risk factor for active tuberculosis (TB). (Kotlarsky, Pavel, et al. 2015) Thin and thick mucus often fails to alert patients in China, who often think of it as the consequence of cold weather or smoking. On the contrary, they are not only related to the lungs but also possibly to the whole gastrointestinal system.

Sweat

Diabetes itself makes it hard to maintain a steady body temperature. Excessive, insufficient sweat or sweating at odd times are strong signs of many complications. Hyperhidrosis is very common among T2D patients. But it is still unclear when it occurs and what the underlying causes and effects are on the internal organs. Sweating speeds up the deterioration of organs by driving T2D patients to drink and urinate more. Abnormal sweating is one of the earliest detectable neurophysiological abnormalities in small fiber peripheral neuropathy. (Simpson, John 2018)

Heartbeat

T2D patients often suffer from shortness of breath, sweating, rapid and irregular heartbeats, which are all symptoms of heart diseases that might be directly related to the spike of blood glucose. They may also be directly related to sleeping, emotional and digestive problems. Without such knowledge, people may suspect straight away that they are suffering from heart troubles. Recent observational studies indicate the associations of insulin treatment with an increased risk of developing or worsening pre-existing heart

failure with higher mortality rates, but with little evidence. (Didangelos, Triantafyllos, and Konstantinos Kantartzis 2020)

Pains

T2D patients with difficulties in glycemic management and following a recommended exercise plan often have chronic pains. (Krein, Sarah L., et al. 2005) Headache is common among T2D patients due to hypertension and hyperglycemia. Toothaches and dental problems are high at risk when the blood sugar is poorly controlled. T2D is also associated with higher pain severity in people with localized osteoarthritis. (Alenazi, Obaidat, Alshehri, Alothman, Gray, Rucker, Waitman, Kluding 2020) Findings by Lorenzo, et.al suggest that uncontrolled diabetes may contribute to the development of chronic back pain. (Rinaldo, Lorenzo, et al. 2017)

Weight changes

Insulin causes significant weight gain and may also cause serious episodes of hypoglycemia. (Didangelos, Triantafyllos, and Konstantinos Kantartzis 2020) Both sharp weight gain and loss in a short period are the results of poor control of blood sugar. Some people with T2D regard weight gain as a positive sign of being healthy especially when their complexion is good. One study by French S, et.al. demonstrated that the risk of diabetes was twofold higher in the participants whose weight fluctuated compared to those with stable weight or moderate fluctuation in a short-term follow-up. (Park, Kye-Yeung, et al. 2019)

Strong emotions

Diabetes distress is a prominent issue in people with T2D which is associated with female gender and comorbid depressive symptoms. It is important to consider the relationship between diabetes distress and depression, as we look into the significant overlap between conditions.（Perrin, et al. 2017） When the glucose level is out of control, people with T2D become moody without being aware of their anger, irritability, sadness, and aggressiveness. They don't want to talk to people and become upset very easily, which makes communication with others very difficult. Having trouble concentrating or thinking clearly makes them nervous and pessimistic. Their low energy level often makes them very frustrated and tired. In such a state, they need directions to control their daily emotions. Doctors need to know what is going on in the internal organs instead of just taking it as a psychological issue.

Sleeping problems

T2D has shown to be associated with a higher incidence of sleep disorders, which may be due to the disease itself, secondary complications, or the associated comorbidities. (Khandelwal, Deepak, et al. 2017) Both high and low blood sugar cause various sleeping problems: having trouble falling asleep, very shallow sleep, short sleep, and waking up at night. Poor sleep can bring about many problems to people with T2D, and be a very strong trigger for them to seek solutions.

Leg swelling

Swelling in the lower body including legs, ankles, and feet caused by a buildup of fluid in the body (Water Retention) is a common symptom and one of the benchmarks of T2D. Other symptoms that occur at the same time will change our understanding of the functions of some internal organs. Diabetic muscle infarction (DMI) is a rare microvascular complication of spontaneous ischemic necrosis of skeletal muscle in patients with poorly controlled diabetes. (Seaman, Callie, et al. 2019) As a less commonly reported complication due to poorly controlled T2D associated with multiple end-organ microvascular sequelae, the occurrence of painful swelling of muscles, particularly of lower limbs, should raise suspicion of DMI. Increased clinical awareness is important for early recognition, particularly in a diabetic patient presenting with a painful thigh or leg swelling. (Jevalikar, Ganesh, et al. 2019, Grigoriadis, et al. 2000)

These triggers, the high alerts on the physical changes in what people with T2D can see and feel in their daily lives, are the causes of all different kinds of complications. They can push T2D patients to check how serious their problems are and work much more effectively than "motivations" just for monitoring the blood sugar without the information about their daily problems and the needed guidance. As these triggers are all connected with the internal organs, the patterns found in the future will build up a knowledge pool that will not only navigate patients to understand their conditions and the needed actions but also provide the evidence for the doctors' timely intervention, treatment, and research.

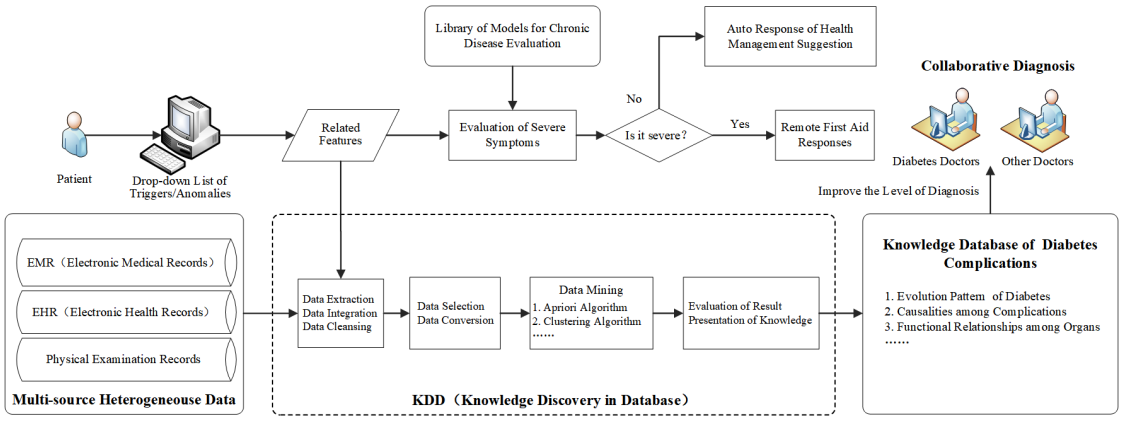

Figure 4: The framework for diabetes patient management and knowledge discovery based on Knowledge Discovery in Database (KDD).

4 THE FRAMEWORK FOR T2D MANAGEMENT AND KNOWLEDGE DISCOVERY

With a patient-controlled interface, this framework integrates patient-generated real-time data with the EMR, EHR, and physical examination records. By using the anomalies of T2D patients in their daily lives as triggers, patients go through and check all thesymptoms, correlated with the internal organs, they are suffering at the moment. For serious cases, patients will be required to upload related evidence that will be analyzed by the system to support the doctors' decision-making. If not, the system will give suggestions on their management. The aggregation of these data will gradually identify the risk factors for early intervention and unveil the underlying biological pathways of T2D complications. New patterns and their pathologies will be captured, analyzed by the system, and stored in the knowledge pool, which will paint an overarching picture about the relationships between the triggers and the causalities on the evolution of T2D complications.

To systematically place the data in the hands of patients, they need to log in with any of the personal data like the name or ID number with the most recent records of their glucose level and blood pressure. To help patients pin down their problems quickly, the drop-down list of the triggers in the system will remind them of the anomalies they may have at the moment with all the related symptoms that are used as part of data input. When acute and severe symptoms are marked under one trigger, patients will be guided to check for other related symptoms and asked to upload pictures and videos if the evidence is needed. Even if they don't have serious physical problems, these triggers can still serve as reminders for them to check about their current conditions for learning, risk management, and prevention.

Behind the triggers, the mapping of all the related symptoms to the corresponding internal organs is the most basic rule of this framework. The symptoms should be classified by their severity and body parts. All the input symptoms behind each trigger start with the ones that are very closely related to T2D, guiding patients to check other possible symptoms that are not directly related but common with complications. Many of the symptoms in one group may overlap with those in others. For example, strong thirst, a very common symptom of T2D, may also be caused by xerostomia or long-term diarrhea. Weight loss, another strong alert of T2D, may also be caused by inflammatory bowel disease. In other words, one symptom may trigger patients to go through many other ones to help form the picture of the evolution of T2D complications.

As T2D complications affect all organs, all the input symptoms also include those of different complications that correlate with the corresponding internal organs. (Alicic, Radica Z., Michele T. Rooney, and Katherine R. Tuttle. 2017) Supported by the known symptoms and their relationships with the internal organs, the output of data mining can be of high accuracy. The patterns captured can be various with the "1 to 1", "1 to n", and "n to 1" relationships between symptoms and organs, organs and organs. With the increase of users over time, new patterns of T2D and the complications can be discovered and verified. Over time, a network of disease connections

can be formed for doctors, researchers and machine learning models to learn and apply. Across the board, all the patterns captured in the future will give us full pathways of T2D progression and complications. Some will fill up the gaps about the evolution of all the known end-stage complications of diabetes nephropathy (DN), diabetes retinopathy (DR), diabetic foot, cardiovascular disease, and stroke. The different stages will be clearly marked with the corresponding triggers at different times, which link up all the symptoms that are related to the internal organs. The patterns of respective phases of complications will pave the clear paths of how they reach the final, irreversible stage.

The associations between and among the internal organs brought about by the triggers at different times will, first of all, give us answers to the current puzzles of the end-stage complications. The patterns about the retinopathy, for example, will clearly show how the renal injury precedes retinal damage apart from the fact that the level of renal impairment is proportional to the level of eye damage as DR and DN has a unidirectional correlation (Sulaiman, Mahaboob Khan. 2019). These can help find new markers for designing clinical trials that evaluate clinically pertinent endpoints (e.g., glomerular hyperfiltration, inflammation, and fibrosis) (Powell, Cooksley, Hanson , Searle , Halliday, Powell 1988), and even expand our knowledge on the association between metabolic changes and DN. Some of these patterns will help explain why the prevalence of chronic kidney disease (CKD) in T2D patients has not witnessed any decrease in the last two decades and lead to the identification of additional factors in its progression despite the aggressive blood sugar control (Pearce, Ian, et al. 2019). Others will help evaluate the findings with clinical manifestations before kidney damage becomes irreversible that can clearly show whether there is an association between non-alcoholic fatty liver disease (NAFLD) and progression of diabetic nephropathy (Hum Pathol 1989).

The collected symptoms correlating to the changes of specific internal organs behind the triggers will probably reshape our understanding of the functions of each individual one. Here we can take the liver for example, because it is consistently associated with other complications of T2D with the severity of DR linked to a higher risk of the presence of, or developing other micro and macrovascular complications as well as a strong predictor of stroke and cardiovascular disease. (Itoh, Yougel, Kawagoe 1987) Apart from the answers for the prevalence of NAFLD in diabetes estimated at 34–74% (Diehl, Goodman, Ishak 1988, Pinto, Baptista, Camilo, Valente, Saragoca, de Moura, Adami, Chow, Nyren, Berne, Linet, Ekbom, Wolk, McLaughlin, Fraumeni 1996, Wanless, Lentz 1990), the emerged new patterns will help explain why the incidence of cirrhosis or severe fibrosis show a significant increase with a 2.52 SMR (standardized mortality ratio) or a 6.84 SMR in the patients going through insulin treatment (Wideroff, Gridley, Mellemkjaer, Chow, Linet, Keehn, Borch-Johnsen, Olsen 1996). They will also help us understand why there is a fourfold increased prevalence of hepatocellular carcinoma in patients with diabetes as well as an increased prevalence of diabetes in patients with hepatocellular carcinoma (Fujino, Mizoue, Tokui, Yoshimura 2001, El-Serag 2004, El-Serag, Everhart 2002, Chan, Truman, Gurwitz, Hurley, Martinson, Platt, Everhart, Moseley, Terrault, Ackerson, Selby 2003). The functional changes going on in the liver along the course will give us ideas on how acute liver failure has appeared to be increased in patients with T2D. (Tolman, Fonseca, Dalpiaz, & Tan, 2007) Liver, with so many overlapping symptoms with T2D such as fatigue, mood disorders, (D'Mello, Charlotte, and Mark G. Swain 2014) weight loss, abdominal pain, leg swelling, bleeding, and shortness of breath, will probably become the real culprit of T2D. Its deterioration and dysfunction can be the cause of the end-stage complications and the deterioration of other organs. If liver stagnation can reveal itself through depressive emotions, pain in the chest or flanks and a tendency to sigh often (Wei et al. 2018), the overlapping symptoms correlated to emotions may all relate to liver dysfunction.

The vertical patterns behind each trigger, like the trigger of emotions, will probably extend or even change our boundaries of medical science. Likewise, the patterns behind the triggers of heartbeat and panting, which can be directly caused by hyperglycemia, can be a strong sign of T2D management failure rather than that of cardiovascular diseases. And the pattern behind the trigger of urine problems may partially explain the leg swelling troubles of T2D patients. The changes of stool from normal to pebbles or diarrhea may not have a direct relationship with the underconsumption of vegetables and fruits, or the inflammation of the bowels.

All the causalities captured by the system together with the known relationships between the internal organs and the known symptoms will largely cut short the path and time on the future research for solutions. These outcomes will far exceed the goals that past machine learning methods tried to achieve in medicine to help physicians anticipate future events

at an expert level with the information well beyond the individual physician's practice experience. (Rajkomar, Alvin, Jeffrey Dean, and Isaac Kohane 2019) At the population level, the same type of forecasting can increase the utilization of health care services and enable the identification of patients with chronic diseases who will soon have high-risk conditions. (Rajkomar, Alvin, Jeffrey Dean, and Isaac Kohane 2019)

All the patterns and causalities will be stored in the knowledge pool for comparison with the initial diagnosis, which will include those of the known and newly discovered complications, the development of one specific or one group of symptoms related to an organ, the functional relationships between and among organs and how they work as a whole system in the human body. The discrepancies from the patterns can be reviewed together by doctors for better understanding and solution optimization. The curated data sets with newly uploaded evidence can be of great value for regional prescribing practices and at the same time, relevant variables will be automatically extracted for ease of use.

5 CONCLUSIONS

The knowledge pool will be continually enriched and enlarged when this framework is applied to the management of other chronic diseases like cardiovascular disease, respiratory disease, chronic liver disease, chronic obstructive pulmonary disease, chronic kidney disease, cancer, arthritis, and so on. The overlaps and relationships within each path of the development of chronic disease symptoms and complications can be discovered and classified, like those of Type-2 Diabetes, for earlier intervention and more effective management. The focus of the future research is to look at the changes of the internal organs vertically and horizontally at the same time. The emerging patterns and correlations among diseases and organs will enable future research to become even more targeted and translatable. With a broadened view and the support of the knowledge discovery framework, concerted and collaborated consultations will become much more accurate and effective for clinical diagnosis and treatments. The underlying relationships with the pathological changes of the internal organs will bring about many new insights and even broaden our view of medicine. Most significantly, the world of the western medicine and TCM can be bridged up for productive collaborations and co-operations.

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