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Type 2 Diabetes Treatments in Countries of Different Economic Status

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Abstract

Diabetes is a global epidemic disease (approximately 1/10 of human patient population ranging from 17-70 years suffering from diabetes). Its influence and damage to human health and death is beyond doubts. Early diagnosis and treatment for diabetes plays key role in determining human life-spans. However, only half of diabetes patients aware their physiological condition worldwide and want to takes medication afterward.

After several decades hard work, the condition and treatment of type 2 Diabetes Mellitus (T2DM) has been improved in major part of worldwide. However the T2DM therapeutics and financial supports are staggering for the limitation of medical knowledge and therapeutic curability more recently because the global T2DM epidemics are still accelerating. The study of causality, pathogenesis, complications and therapeutics of T2DM remains to be progressed at this moment. Disease complication is still an issue.

Entering into this millennium, either piecemeal pathways (idea driven) or curability exploration (human genomic study)-including T2DM genotypic-phenotypic translation, modern diagnostics, pharmacology, drug developments, traditional medicine, personalized medicine and so on are discussed.

Major patho-therapeutic relationships are highlighted in different forms including anti-diabetic therapeutics, etiological approaches, drug development framework and basic scientific explorations in this article. Molecular, physiological, behavior and environmental pathways and influence are especially outlined.

Keywords: Anti-diabetic therapy; Insulin-derivatives; Therapeutic optimizing; Herb medicine; Diabetic complication; Medication economics; Drug trials.

Introduction

Disease definition between east and west

Diabetes (diabetes mellitus, DM, in west) is a disease characterized with persistently high blood glucose level caused by inadequate or dysfunction of human insulin [1,2]. “Xiaoke” is a Chinese definition of diabetes describing symptoms of thirsty and high-frequency of urination in patients [3]. However, no satisfactory treatment detail was given in early Chinese books comparing with western countries. Previously, life-style and dietary adjustment was generally mentioned in both eastern and western medical literatures.

Diabetes epidemics

Diabetes is a global epidemic disease (approximately 1/10 of human population ranging from 17-70 years suffering from diabetes) [4]. Overall, 90% of these patients are type 2 diabetes mellitus. Its influence and damage to human health and death is beyond doubts. Early diagnosis and treatment for diabetes plays key role in determining human life-spans. However, only half of global diabetes patients aware their physiological deficits and condition.

After several decades hard work, the condition and treatment of Type 2 Diabetes Mellitus (T2DM) has been promoted in major parts worldwide. However the T2DM therapeutics and

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financial supports are staggering in Low and Middle Income Countries (LMICs) because the global T2DM epidemics are still accelerating [4]. The study of causality, pathogenesis, complications and therapeutics of T2DM remains to be clearly elucidated at this moment. More importantly, disease complication is still an issue.

Roles of insulin

For the symptom of higher blood and urine glucose levels (Diabetes Mellitus), insulin was attributed for all these clinical symptoms and pathogenesis [1,2]. Insulin-based therapy (modern therapy) against Diabetes Mellitus was developed for 50 years throughout world. Diagnostics (blood glucose level test) and treatments (synthetic, phytochemical, herbal, nano- and bio-agents, like leptin and insulin-associates) have advanced pharmaceutical potentialities nowadays and in future.

Categorization of the diseases

Human diabetes is categorized as 4 entities. In the early-stage of last century, diabetes is widely known for insulin deficiency in patients. Now, it is defined as type 1 diabetes mellitus. Insulin-related or supportive treatments are the most important selection for patients with type 1 diabetes.

In the second half of last century, Type 2 Diabetes Mellitus (T2DM) were prevalence and recognized as a major public healthcare concerns worldwide (382 million cases worldwide in 2013) [4]. Table 1 shows the incidence and prevalence of T2DM in worldwide (Table 1). Key risk factors for different types of diabetes are listed for therapeutic classification.

Table 1: The populace and tendency of global cases of T2DM.

Global T2DM cases worldwide (million)					
2000	2005	2010	2015	2020	2025
151	220	285	415	500	>540

The incidence of T2DM in China (98.4 million in 2013) and other developing/developed countries (65.1 million, India, 24.4 million in US, 11.9 million in Brazil in 2013) have been all growing due to unavailability of anti-diabetic therapeutics (unnoticed cases, ineffective feature of anti-diabetic therapy and growing age of average human populations) [4-9]. T2DM treatments are yet to be among unnoticed patients worldwide. This article addresses some of them, especially for new ideas, drug development and latest insights into T2DM treatments and managements.

Biological and molecular process for T2DM

Possible pathway for the initiation of T2DM

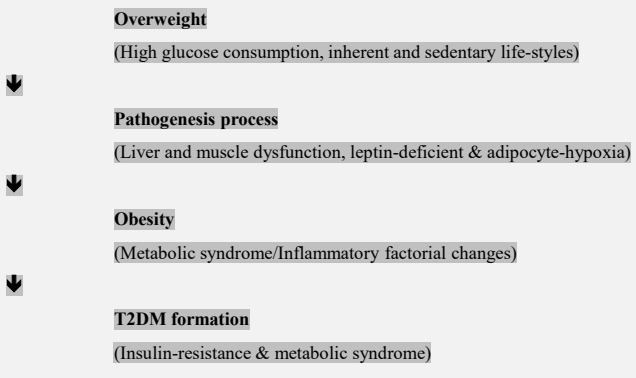

Figure 1: The most frequent pathway & cascade for T2DM induction.

In the long-course of T2DM induction and progress (Figure 1), it shows that a great number of risk-factors and drug targets can be investigated for disease progress and management.

Generally speaking, many other factors (chemical, biological or environmental stress) could trigger pathways and cascade of T2DM occurrence, like diabetic animal model establishment [10,11] (Table 2 and Figure 2). Table 2 shows lines of chemical, genetic, cellular, physiological and pathological factors that may possibly involve in T2DM initiation and pathogenesis. People found out many T2DM causalities among growing number of human population, especially genetic and environmental aspects.

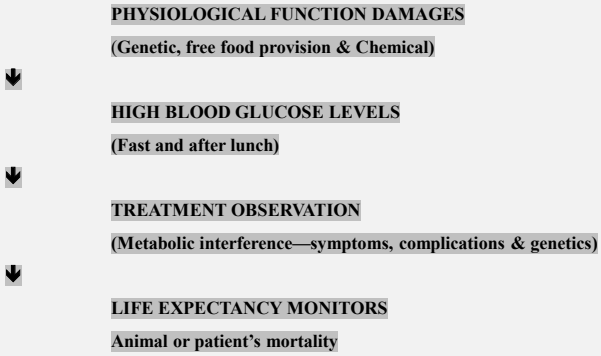

Figure 2: Animal model establish for T2DM.

Table 2: Possible categories of risk factors for T2DM relevance.

Etiology	Possible pathological pathways	References
Biochemical	Hormone regulation Growth factor over-excretion Leptin Insulin Adipocyte-hypoxia Adipocyte-respiration Pituitary hormonal synthesis and secretion Toxic compounds Viral Other drugs	[4-11]
Physiology	Old age Liver dysfunction Inflammation Obesity Insulin-resistance Sleep problems Energy homeostasis Hypothalamic circuit	[6-8,12-18]
Food & life-style	Palatable food (processed foods) Free-accessed to foods Sedentary occupation Long-term TV watching Alcoholic Exercise deficiency Sweet-addictive	[4-5,12-16]

Frontiers for new managements

Importance of early diagnostics: Developing type 2 Diabetes Mellitus (T2DM) undergo a lengthy and complex process from disease onset into symptoms and complication (cardiovascular or depression) in susceptible human beings. As a result, the pathogenesis cascade must be noticed at the earliest or before high blood glucose levels in patients. For these late-diagnosed patients, normal life-expectancy will be difficult.

Many healthy measures (regular exercises, dietary or life-style adjustment) can be really work in disease onset and ongoing stages but never omnipotent. Systematic treatments will be utilized. However, long-term drug utility should be done in a lot of patients. It is cumbersome and difficult to follow.

Some well-established, long-lasting and far-reaching medical education, diagnostics and animal models for diabetes are shown in larger human populations in order to early management of diabetic progression and the reduction of human mortality [1,2]. Due to asymptomic characteristics in early stages of metabolic syndromes, such as T2DM, early diagnostics is in inevitable [2-4].

People should be aware that high calorie food consumption is not the only factor to induce T2DM, some other unfavorable factors, such as habitually heavy drunk, genetic mutations, toxic compounds-induced or sleep problems etc [12-14] can also trigger the events of T2DM. Besides, some other causes (etiologic factors) are still unknown to us. Thus, regular medical check-up for blood glucose levels should be carried out for people more than 40 years old, especially for people in LMICs. It is decisive to human age elongation and life-quality promotion. Figure 2 shows different ways to build anti-diabetic animal models. This process means a lot for understanding human diabetes in various molecules and pathways.

Molecular mechanisms

Overall situations

A great number of risk factors of either inheritable features (genetic or molecular aberration) or environmental stresses (high calorie dietary consumptions and sedentary lifestyle) are discovered. To facilitate the elucidating of molecular mechanisms, patho-therapeutic relation should be clarified [19]. As a matter of factor, a deeper understanding of pathologic and pharmacologic pathways of T2DM is necessary and note worthy. The exploration of molecular pathways and mechanisms is useful to treatment updating and cost-effective consideration according patient's financial status.

Glucose derivatives in foods

In the initial stage of drug development, interfering or sabotaging and digestions systems in glucose absorption by structurally similar carbohydrates in foods is popular. Until now, this kind of glucose metabolically competitive therapy in pharmaceutical sciences is less important [20-22]. However, they are popular in food consumption. Owing to a wide-range of disease causalities, anti-diabetic therapeutics must be multitude targets and optimized to individual patients [23].

General therapeutic targets

A number of disease complications, such as kidney disease and foot ulceration are detrimental for patients and human mortality. Regular therapeutic mechanism and putative drug target studies are highlighted in following pathways;

What is the therapeutic outcome and differences between patients with T2DM of various causalities, complicates and avoidance?.

What are genetic-molecular relationships and mechanisms between high blood glucose level and different disease complications?.

May a known variety of T2DM target suitability to different individuals (basis for personalized medicine)?.

Can we successfully predict what kinds of diabetic-induced complications will emerge under specific conditions of patient stages with T2DM?.

Why are we less effective to manage diabetic-induced complications in the clinic? Must it be treated earlier or others?.

Genetic and molecular profiling

In order to update therapeutics (targets or personality), critical questions of how genetic, molecular, physiological, behavioral and environmental profiling of disease-associated pathways and hallmarks must be enlisted and pursued one by one [21,23,24]; Advanced therapeutic strategies will be invented experimentally and clinically.

Taking account individual variability in genetics, environmental and life-style, might create some effective medications by separately validity in the clinic?

What is the core variability by different types of anti-diabetic therapeutics in large human populations and data analysis worldwide?.

Can curable therapeutics be widely achieved in patients with T2DM?.

Without fully understanding of patho-therapeutic relation, doctors cannot control the disease progress for patients with T2DM. These therapies are less effective to diabetic-induced complications. However, this is a key issue for therapeutic failure and human mortality in range of middle age. This avenue of early detection and treatments is inevitable for patho-therapeutic study for type 2 diabetes.

Genomic study

From the point of view of molecular biology, T2DM might be generated from genetic alterations/ interaction, environmental stress and unhealthy life-style. Personalized Anti-Diabetic Therapy (PADT) may be developed by better diagnostic and therapeutic studies for T2DM.

Pharmacogentics (PG) [22-25], one of the widest utility of Personalized Medicine (PM) has a great potentiality for drug selection and dosing in clinical trials. To accomplish with PG for T2DM, human genetic/pathologic information must be detected before therapeutics.

With the advent and mature of Next-Generation Sequencing (NGS) technology [24], this kind of human genomic study go exponentially in quality and quantity [25]. But, how can we handle these kinds of human genomic information without regulation and damage the image of patients. An ethical question of agreements between patients and healthcare providers should be strengthened year by year [25]. Regulation should be made to more doctors, not the patients. Currently, the "loss-of-function" genetic mutation of leptin, insulin and their receptors are widely explored in global labs and hospitals. These kinds of genomic studies will greatly accelerate diabetic therapies in broad-ranges.

PG study and application

PG for normal diseases is divided into two domains (metabolism enzymes and targeted molecules) [26]. At this stage of technical capability, we could not determine all relevant molecules (metabolism enzymes and aberrant key molecules)

in same tests clinically. We could only determine several molecules in clinical settings due to the consideration of feasibility and costs. Technique inadequate also undermines the outcomes of diagnosis and therapeutics. The final solution for that will be achieved by scientific and technical advances.

The test of genes of metabolism enzymes is designed to consider drug dosing (pharmacodynamics or pharmacokinetics domains)-detecting polymorphisms of human metabolic enzymes [26]. These processes are familiar by hospital doctors. As the unpredictable nature of disease-related molecular alterations and metabolic abnormality, genetic or bioinformatics detection of various diabetic-related pathways is the key foundation of PADT study (Figure 3). Figure 3 represents the outlook and possibilities of PADT applications in the clinic. This type of PDT may be effective by novel treatments in the future [23-25].

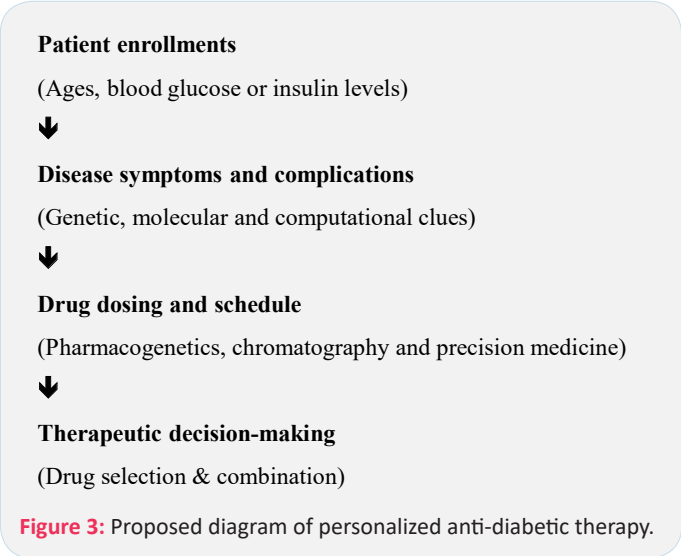

Figure 3: Proposed diagram of personalized anti-diabetic therapy.

Beyond early diagnostics of T2DM, different modern diagnostic approaches (cutting-edge and popular) are inevitable. Of course, this kind of diagnostic advances for T2DM-induced disease progress study should be novel designed, such as avenues of early, simple and low cost for LMICs. While modern diagnosis (genetic or molecular profiling) should be utilized for larger population gradually.

Molecular and physiologic pathways

Molecular and physiologic pathways for T2DM develop suggest multitude risk factors (inside and outside). We associate them in Table 2. Following deductions are represented;

Neural activity and circuits that control the appetite of patients located onto brain hypothalamic area [21].

Abnormal metabolic conditions; their dysfunctions in adipose tissues, livers, muscles and other human metabolic organs are observed [23].

Hormonal synthesis, secretion and resistance, such as insulin, leptin, cytokins and growth factors play key roles for patients' obesity and diabetes develop [5-16]. Their synthesis, secretions and functional resistance can be used for early diagnosis and treatments of T2DM.

Energy homeostasis imbalance; a lot of patients with T2DM have an experience of food control. However, it is commonly failure and leads to further overweight. These types of food management are personalized.

Treatment convention is divided in countries of different financial condition. Human energy balance will decide human body weight gain or loss and further affect blood glucose levels. This energy issue is very important for T2DM progress and managements [23].

Co-morbid and association

Apart from genetic or molecular targeting and profiling, some co-morbid association should be noticed, such as metabolic diseases [27-29], aging [30,31], neurodegenerative diseases [32], cancer [33] and others. It is still a mystery why old people show higher blood glucose level that is similar as T2DM. The associated pathways between blood glucose and people aging should be further investigated in the future.

Pharmaceutical industry and ecomonics

Finance and treatment variations

The T2DM diagnosis and treatment is divided among countries of different socioeconomic status. In industry countries, more types of diagnosis and therapeutics can be optioned. In order to be more effective to control the disease, advanced techniques or new drugs will be chosen. Likely, the dose of insulin or its derivatives can be used widely and conveniently (one dose a day) for advanced stages of diagnosis and treatments in wealthy countries.

However, in LMICs, only elementary diagnosis (fast or after meal blood glucose level tests) and treatments (chemo- or herbal drugs) can be selected. Some costly drugs (genetic or molecular modified drugs are not easily accessed to general patients. In these countries, herbal medicine (HM, such as sage, stevia, ginseng and robat root) is widely accessed due to reasons of belief, low-cost and long tradition) [34-39]. Systematic comparisons for efficacy and toxicity between two streams of countries will be useful for therapeutic comparisons and updating. Until now, there is lack of therapeutic selection and comparisons.

Herbal drugs

Approximately 50,000 to 80,000 herbal species have medicinal properties worldwide [35]. More than 500 species are reported to be associated with anti-diabetic potency. A lot of articles reported functional and therapeutic data and outcomes in experimental settings and clinical practice (ancient wisdoms, medical knowledge from doctors of countryside and tribes). This tradition of HM is growing lost and should be kept in the future.

Currently, only a few of medicinal herbs have been licensed in global markets for T2DM prevention and treatments. Likewise, it is one of the major avenues for therapeutic promotion and drug development in the future [1,2]. Most of therapeutic intervention data from anti-diabetic herbs came from tradition, religious or local doctors. This type of knowledge is shrinking due to loss of these traditions and clinical applications [36]. These relations of herbal or folk medicine should be built and kept.

Multitude biochemical pathways, such as antioxidant activity, insulin synthesis, secretion and resistance of glucose uptake can determine glucose production regulation and consumption from muscles, hepatocytes, neural axis, anti-inflammatory activity and so on in a variety of references [40,41]. However, herbal drugs are not allowed for therapeutic purpose in western countries because of the requisite of high-quality and com-

plexity of drug prescription in the clinic. From pharmacological perspective, the therapeutic study for HM needs to aim at more specific drug targets and whole body blood glucose production regulation in clinical trials. Many animal diabetic models might not be the best vehicles for clinical anti-diabetic therapies for HM. New animal models should be established for solving such dilemma.

To better utilize herbal drugs, some principle of traditional medicine for diabetes should be properly established and pass down [1,2]. Combinations and integration of anti-diabetic therapy of cutting edge (modern pharmaceutical options) means a lot and future trend. As the safest and first-line anti-diabetic therapeutics, insulin and insulin-derivatives can be used medication in both type I and type II diabetes treatment according to different features of clinical situations and stages [12].

Insulin-based therapies

Insulin-based therapy needs to improve for clinical feasibility. From pharmaceutical perspective, widely insulin-utility needs syringes and human-body injections, in which may result in treatment inconvenience. Many insulin-therapies have been improved in diabetic therapies (one-injection a day) for the purpose of liver and kidney toxicity avoidance by chemical or herbal drugs.

Therapeutic feasibilities for different types of diabetes

Theoretically, a great number of drugs can be useful worldwide. Table 3 outlines parts of these therapeutic options in the clinic. Despite wide-ranges of drug developments, clinical T2DM treatments are commonly incurable [2]. Most therapeutic options are effective on symptom control (stable of blood glucose levels) yet life-long medications for T2DM patients. After all, we need to know not only patho-therapeutic relations, but also financial states of patients in the future (Table 3).

Table 3: The recommended therapeutic optionsin clinical diabetic treatments.

Drug and therapy	Mechanisms of action	Adverse events
Insulin and its derivatives	Glucose metabolisms	Not significance
Sulphonylurea	Stimulate insulin secretions	Gastrointestinal (20-30%), Infections (20%)
Biguanide (Metforrnin)	Decrease amount of sugar productions by liver	Metabolisms
Acarbose Voglibose	α-glucosidase inhibitors	Gastrointestinal (20-30%)
Pioglitazone	Receptor agonists	Heart failure (1-5%), Bladder carcinoma (1-2%)
Sitagliptin Vidagliotin Saxagliptin	Dipeptidy peptidase IV inhibitors	Injection
GLP-1 analogues	Nature pepetic C	Injection
Gene therapy	Insulin-formation	Under-investigation
Pancreatic transplantation	Recovery of pancreatic function	Difficult to implement
Vaccine	Infections	Not obvious
Gastric bariatric surgery	Obesity	Expensive
Orlistat	Obesity (pancreatic lipase)	Only drug for obesity
Propolis	Disease complication	No
Natto	Vascular softness	No
Herbal drug (>500)	Variable	Variability
α-thioctic acids (Lipoic acid)	Disease complications	Not obvious
New anti-diabetic drugs	SGLT-2 inhibition DPP4 antagonists	Under investigations

Apart from herbal drugs, bee products (Propolis) [42] and fermented soybean (Natto) [2] were also introduced in China and Japan for symptom alleviations and immune functional promotion.

Clinical strategies

Life-style adjustments and combination

Regular exercise and food restriction (life-style adjustment) is an effective way for lowering blood glucose levels and disease complications for patients [43]. As usual, combination of life-style adjustment and anti-diabetic drugs is widely recommended by the administration of both American Diabetes Association (ADA) and European Association for Study of Diabetes (EAST).

Table 3 shows a number of therapeutic options. Like other chronic diseases, more than one therapeutic option in clinical trials are frequently more effective in the clinic. Generally, drug combination is more welcome for refractory chronic disease comparing with mono-therapy [44-46]. It is a new concept of whether a systematic approach is helpful for combination principle discovery and establishment [47].

Combination theory and principles

Given wider spectra of clinical symptoms and complications among different individuals, it must seek different formula of drugs and combination principles for high-quality therapeutics for chronic diseases. To build up high quality of drug combination strategies, clinical anti-diabetic treatments might be updated constantly in the future.

Grounded theory for medical or pharmacological knowledge and combination is still of great interests and significance. In the future, drug combination in the clinical trials should be mathematically analyzed before drug selections, combination and dosing optimizing in different clinical conditions. Of course, this type of medical work and theories must be based on clearer understanding of diabetes pathology and pharmacology, like

cancer and HIV/AIDS treatments and patient's favorability [44-47]. After such pharmacological and clinical comparisons and possibility studies, drug combinations for T2DM might be transformed from random regimes to computerized selection systems and finally go personalized and satisfy by patient's choice and drug adherence.

Disease complications

Unavoidable, diabetic-induced complications are multitude and sometimes very serious in patients with long course of T2DM progress and therapeutic adherence [48]. Large parts of disease complications (eye, feet or kidney diseases) are difficult to be successfully reversal-usually only slowdown of a disease complications after routine interventions-usually incurable [49-52]. Diabetic-induced complication treatments should be emphasized as early as possible. Majority of diabetes complications are represented in Table 4. Thus new generations of anti-diabetic therapeutic agents must be designed in this respect. However, this strategy is difficult to achieve so far (Table 4). Evaluative architecture should be promoted.

To work with new generations of medical practice, early diagnostics might be helpful [2-4]. Certainly, these kinds of diagnostic trends should be targeted and less cost in the future.

Table 4: Major diabetic-induced complications in patients.

Complication locations	Specific types and symptoms
Metabolic	Cardiovascular Overweight/obesity Muscle malformations Ulcer of lower limbs
Immune dysfunction	Different types of infections Other diseases
Eye complications	Visual damage and blur Cataract Fundus hemorrhages and vessel leakage
Kidney failure	Nephropathy
Central nerve systems	Brain retardation Cognitive impairments

Future approaches

Diagnostic convention

Expanding pathological knowledge to broader ranges of people should be focused on genetic or molecular approaches. Advanced diagnosis (genome wide association study, GWAS and multi-omics profiling) between patients and normal people should be speed up [53]. Deeper understand of T2DM pathotherapeutic relations could bear new grounded theories and suit for more patients of both developing and developed nations.

Therapeutic promotion

Genetic or molecular study of disease progression, drug pharmacology, mechanisms of action and therapeutic balancing between drug activity and toxicity have great potential for medical and pharmaceutical innovations. Establishing personalized anti-diabetic therapy protocols in the clinic will be profitable for both drug developers and patients. The development of higher therapeutic-index and cost-effective drugs, such as natural chemotherapeutic anti-diabetic drugs can benefit more patients in LMIC countries [36-39]. Budget control in drug developers and clinical treatment selections in the next generations will be available quickly [54-58], such as SGLT2 that can improve glucose content and reduce cardiovascular events simultaneously.

Nursery participation

To update anti-diabetic treatment, diagnostic and treatment selection is important factors in poor counties. In poor countries, people do not have enough money to seek medication from doctors. However, blood glucose detection needs medical expertise. Yet, nurses can take part medication usually made by doctors, such as regular blood glucose determination and drug providing [59-61]. Nonetheless, the cost for nurses can be much cheaper than doctor's. In LMICs, nurses can be useful option for patients with T2DM. These specialized systems can be popularized in many poor countries worldwide.

Computation and drug develop

Global cooperation is inevitable, especially invitation of mathematical majored students and scholar in this medical campaign [62-64] and mathematical solution of disease risk factor analysis, symptom alleviation and diagnostic advances. Many mathematic equations, like following (Equation 1) will help discovery toxicology knowledge for diseases and treatments.

Mathematics study of diabetic treatment, blood glucose reduction and undesired complications is multiple and complex, It consists in data simulation, algorithm selection, computation and statistics. Latest progress in technical tools and equation of artificial intelligence can help us to understand more about diabetes. This trend will bear new breakthroughs when techniques and science advances. They will face and calculate both qualitative and quantitative data from experiments to clinics [63].

Computation simulation, docking and mathematics equation now widely undergo new challenge in each area of disease treatment and drug development. Apart from normal pharmaceutical exploration, computer-aids drug design, deep learning and molecular docking are fastest developing areas for drug developments. More or less, they will help patients east and west. Today, the most important topic in this regard is to find suitable genetic or molecular targets for T2DM. New equation is outlined Eq 1 or others as an example in this area.

$$T(P_1.....,P_n)=K\int\int_1^n q(P_n) \quad (Eq\ 1)$$

T; T2DM affected ratio and numbers, θ; risk rates of diabetes in random population, K: some constant

Summary

Balancing between efficacy and costs

Despite a lot of new discoveries, current therapeutic agents (such as insulin and other drugs) are economic burden to patients due to long-term of drug utility (generally >1,000 USD per year for patients in developed countries). Rapid development of medical knowledge, biomedical technology and useful anti-diabetic drugs, especially diabetic-induced complications for patients living in low income countries, is a high priority and of great medical significance [65-69]. With so many new cases each year worldwide, a step closer in treatment is a marvelous thing that can transform into a big difference and breakthrough (a rapid and curable management of T2DM patients) globally.

Treatment diversity and integration

Given too much diabetic components and pathways can be

targeted, a growing number of patents for anti-diabetic treatments all across the world [4]. Growing financial supports from developing countries, such as China and India (higher disease prevalence areas with huge human populations) are benefiting.

As most patients with T2DM (>85%) come from developing countries yet the developed countries have good technical supports and large parts of talented researchers, joint-efforts between developed countries and developing countries seem to be mutual benefits and sustainable. To sum up, win-win policy globally can decide how long we can go through in this medical campaign. After global cooperation, both extremes of human diseased populations and researchers can provide high quality anti-diabetic medications, especially PDT in the future (Figure 4).

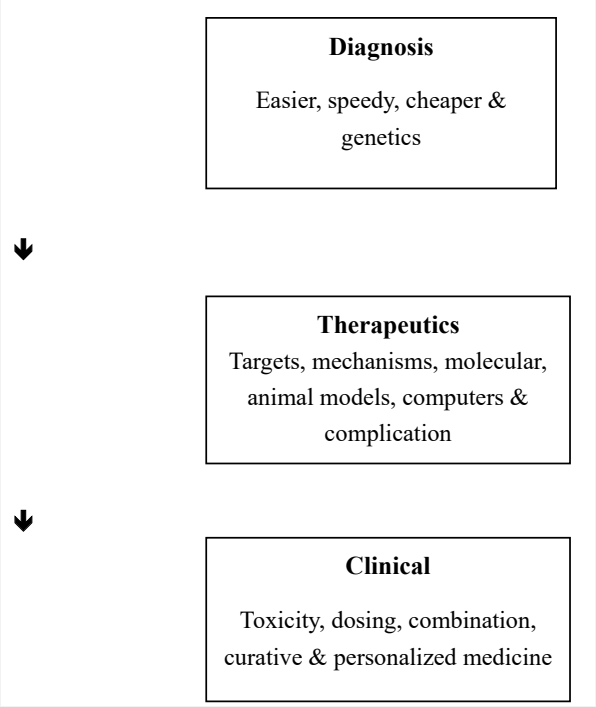

Figure 4: Treatment, drug development and clinical personalization.

Conclusion

Treatment of diabetes is still a medical challenge for pathotherapeutic breakthroughs and ground theory discovery. In the future, new perspectives and scientific investigations will be introduced for changing the landscape of anti-diabetic therapeutics if possible. A lot of therapeutic options need to be better targeted for long blood glucose increase and serious complications by systematic approaches. After that, more effective anti-diabetic drugs will be developed.

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