Path to Personalized Medicine for Type 2 Diabetes Mellitus: Reality and Hope

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Abstract- Type 2 diabetes mellitus (T2DM) is recognized as a public health problem and increasingly prevalent illness. Key elements of the guideline for diabetes care are based on evidence-based medicine approach and apply for population, not individuals. However, individualized care can improve diabetes management. Personalized medicine is otherwise called precision medicine tries to find better prediction, prevention, and intervention for T2DM individuals. Precision medicine in diabetes refers to the utility of genomics data of a patient with diabetes to provide the most effective diagnosis strategies and treatment plans. Over 100 genetic loci influence susceptibility to T2DM. Genomics data together with the potential of other "Omics" and clinical evidence-based data will lead to diabetes care improvement in the context of personalized medicine in the near future. Breakthrough of technologies enables much greater improvements in the understanding of individual variations that may alter the T2DM outcome. This article represents a comprehensive review of current knowledge on the impact of personalized medicine in T2DM.

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Introduction

Type 2 Diabetes Mellitus (T2DM) is a complex disorder involving genetic and environmental risk factors. It has been associated with long-term damage and complications in the eyes, kidneys, nerves and heart (1).

Worldwide prevalence figures estimate that there were 415 million people living with diabetes in 2015 and that by 2040 this number will have risen to 642 million (2). Heritability of type 2 diabetes mellitus is estimated to be 30-70% (3).

Main pathological causes in type 2 diabetes are insulin resistance, decreased insulin secretion relative to hyperglycemia, pancreatic β-cell (PBC) dysfunction, disturbed renal glucose transport and incretin effect (Figure 1). These functional impairments arise through the interplay of genetic and environmental risk factors (4).

Glucose intolerance is a consequence of the addition of these risk factors in the long run and may manifest itself during fasting and or postprandial state. However, American Diabetes Association (ADA) criteria do not recognize identical groups of people at increased risk of T2DM and their susceptibility to complications. For instance, patients with impaired glucose tolerance are at greater risk for macrovascular complications than those with impaired fasting glucose (1,5-7).

A better understanding of the pathophysiologic process and progression of diabetes is to create more capable conditions for the management of patients. Nevertheless, we have not been able to fully answer several questions; how we can predict the incidence of diabetes in persons at risk? How can we predict progression prediabetes to diabetes? What we can do to prevent it and why only some patients with type 2 diabetes show some complications? (8,9).

In the management of T2DM, it has been tried to support insulin secretion and/ or promote insulin action, or decrease renal tubular glucose reabsorption (10,11). The combined recommendations of the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) for the management

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of diabetes patients show a move from a step by step protocol-driven approach to a patient-centered approach by more emphasis on choosing the best treatment for an individual patient (12,13).

Personalized medicine, otherwise called individualized, stratified, P4 or precision medicine, try for better treatment and intervention to the individuals at the right time for the right person in order to take full advantage of this new approach in medicine and decrease harm. The term personalized medicine has been used in diabetes management since 10 years ago. The ultimate goal of precision medicine is to find a potential for integrative treatment and prevention that can benefit from both of them alike, but the obstacles in precision prevention were higher than precision treatment (14). In the context of precision medicine, we are able to have an accurate and precise understanding of the genetic basis of disease that leads to personalized medicine, the umbrella term and the fruit of precision medicine approaches (15). Several other factors such as the completion of human genome project, applying omics data (e.g., genomics, transcriptomics, metabolomics, proteomics, *etc.*), expanded computational power and digital health, large private and national biobanks and worldwide interest, make this an ideal moment in time for burgeoning personalized medicine (16).

Health care professionals in the field of diabetes care have been practicing personalized medicine indigenously for many years, but there are several challenges in applying it in prediction, prevention and treatment of diabetes in the new-fashioned organized form. The entrance of personalized medicine in the area of medical practice needs analytical validation in order to establish the sensitivity, specificity or predictive value of the genomic biomarkers and also requires specific regulatory concern (17).

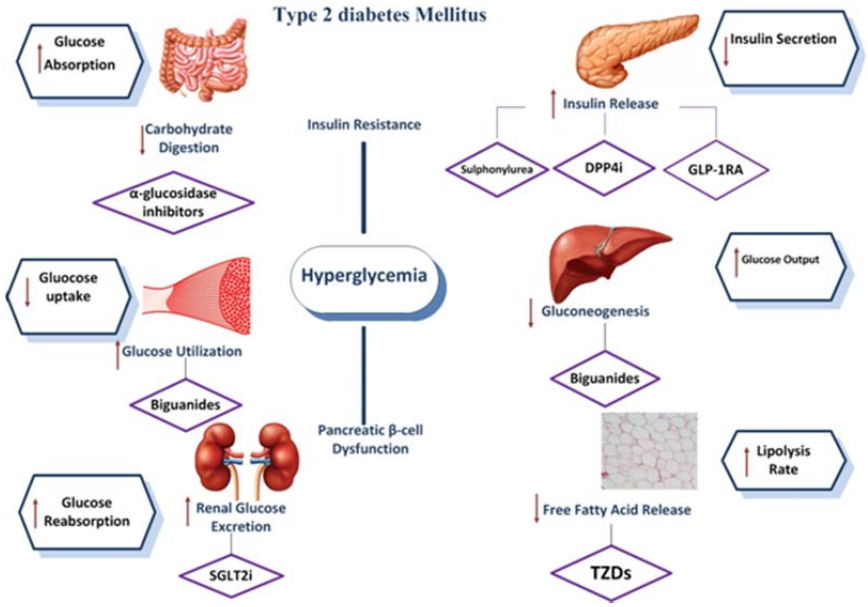

Figure 1. Management of T2DM from a pathophysiological point of view (4,28-31)

Personalized medicine and susceptibility to T2DM

The value of personalized medicine on diabetes will be pharmacogenomics perspective and the role of genetic factors in diabetes diagnosis and in the prediction of complications (18).

Many important resources for precision diabetes medical research have been launched. As a dual effort between NIH and pharmaceutical companies with the aim of precision preventive and treatment for T2DM collected the results from 28 large genome-wide association studies (GWAS) with incident diabetes in Type 2 Diabetes Knowledge Portal (www.type2diabetesgenetics.org); the other one, Insulin Resistance Atherosclerosis Study (IRAS) by supporting of National Heart, Lung, and Blood Institute (NHLBI) have found a possible biomarker for the incidence of T2DM (16).

An outstanding, but the crucial challenge is the ability to combine the disparate results of these resources to provide a comprehensive view of precision diabetes medicine. Many genes have been reported in association with type 2 diabetes mellitus, even though

no single gene region is found for T2DM as for type 1 diabetes (16).

Diabetes care has witnessed remarkable growth whereas oncology pioneered the introduction of precision treatment based on genetics (19).

Heritability of T2DM is well established in different studies and risk of developing T2DM varies approximately between 3-6 if any individual has affected parent or sibling compared to the general population (20).

Meanwhile, we have not completely understood the reasons of different phenotypic presentations and the onset time of microvascular and/or macrovascular complications in patients with T2DM.

Using genetic information and calculating a genetic risk score, based on different genetic variants, may enable us to reclassify patients with T2DM in discrete pathophysiological subgroups, in order to apply targeted preventive or therapeutic interventions.

On the other hand, knowledge of any relation between glycemic control and diabetes complications is assessed in response to intensive glycemic control; nevertheless, in spite of tight glycemic control, some individuals develop complications, whereas others with poor control seem to have some defensive armor which helps them to not develop complications. Therefore, if we can predict susceptible individuals, we could identify more personalized ways to prevent diabetes complications. This will be one the most important impacts of personalized medicine in diabetes care (16).

In combination with genomics , proteomics and metabolomics which examine proteins and metabolites in body fluid respectively may have great potential in the future of personalized diabetes management (21).

Meanwhile, we had to provide an infrastructure for evaluating the "Omics data" and its clinical utility for diabetes management. From this point of view, the personalized medicine in diabetes needs the establishment of interpretable clinical decision system (18).

Pharmacogenetics in T2DM

The treatment approaches for T2DM are very variable. Considering T2DM environmental risk factors, all the strategies can be influenced by lifestyle changes, especially diet and exercise. The ADA has recommended a patient-centered approach to pharmacologic therapy of T2DM. Early intervention and appropriate continuous treatment can reduce the severity of diabetes and related complications. Despite some pitfalls, the quality and quantity of long-term glycemic control can be measured by HbA1c. In T2DM, pharmacological treatment is usually initiated with metformin, but the degree of treatment response could be determined by the genetic architecture of each individual (1,7,22).

Detection of biomarkers to predict treatment response in personalized medicine remains the long-term purpose of pharmacogenomic studies. The terms Pharmacogenetics and Pharmacogenomics are widely used interchangeably.

By considering common variations in certain genes, in the form of single nucleotide polymorphisms (SNPs) in an individual's genetic architecture, pharmacogenomics can promise new drug selection process in order to optimize pharmacokinetics and pharmacodynamics to eventually increase drug efficacy and decrease adverse drug reactions.

Traditionally, the pharmacokinetic approach is focused on some candidate genes related to drug targets, metabolism, and drug distribution. With the development of new technologies, such as whole genome sequencing, pharmacogenetic studies for T2DM have been applying genome-wide approaches to investigate adverse drug reactions and treatment efficacy by interrogating millions of genetic polymorphisms across the genome (4,23).

An essential concern underlying the strength and feasibility of pharmacogenomic studies is the genetic makeup of drug response (24).

Based on the contribution of multiple genetic factors in the etiology of T2DM and variable response to different anti-diabetic agents, there should be an association between genetic architectures of T2DM and the treatment efficacy. Pharmacogenetic studies have been performed to help the understanding of treatment efficacy and adverse drug reactions (ADRs). There is a relationship between the genetic architecture and treatment efficacy of anti-diabetic agents in individual patients, but few strong pharmacogenetics studies have been done in this regard (4).

The practice of clinical medicine as a combination of art and science permit us to appraise each patient on the basis of their genotype and phenotype to develop a personalized care. Management of diabetic patients encounter difficult challenges, as they are a very diverse group of people from different ethnicities, age and various etiology, and variable insulin resistance and beta cell dysfunction (12). On the other hand, clinical application of pharmacogenetics data has not been well established in T2DM due to some limitations including small sample size, availability of data from healthy volunteers without diabetes, lack of precise

definition of drug response and the incidence of drug toxicity (25).

The first-line medication for T2DM is usually metformin. In addition to glycemic control, metformin possesses pleiotropic effects that can reduce the chance of developing diabetes-related complications and mortality (19). The second line oral agent could be sulfonylureas, meglitinides, sodium glucose transporter-2 inhibitors (SGLT2i), thiazolidinediones (TZDs) and dipeptidyl peptidase-4 inhibitors (DPP4i) (1,7,26,27).

Each of these classes of medications has different mechanisms of action (Figure 1). Different genetic variants in the genes encoding drug targets, drug transporters and drug metabolizing enzymes can influence in drug response in the case of efficacy and toxicity (Table 1).

Metformin (dimethyl biguanide)

It was first introduced in the USA in 1995. Metformin counteracts insulin resistance through several insulin-dependent and -independent processes that mainly exert glucose-lowering actions with a low risk of hypoglycemia. Metformin typically reduces HbA1c by 1-2%. The main glucose-lowering effect of metformin in T2DM is a decrease in hepatic glucose output, particularly by suppression of gluconeogenesis and glycogenolysis in the liver (22).

Variability in pharmacokinetics and response to metformin in T2DMs patient could be the result of single nucleotide polymorphisms in the transporters SLC22A1 which encodes the organic cation transporter commonly known as OCT1 and/or SLC47A1 which encodes the multidrug and toxin extrusion known as MATE-1 (4).

The OCT1 gene encompasses multiple genetic variants (rs12208357, rs34130495, rs34059508) that are associated with decreased effectiveness or no efficacy of metformin (32,33).

Two distinct variants (rs2289669 and rs8065082) in SLC47A1 have separately revealed an increased effect of treatment by metformin (34).

Metformin Genetics (MetGen) Consortium reports a three-stage genome-wide association study (GWAS) on rs8192675 in the intron of SLC2A2; they have found this SNP as a potential biomarker for the stratified medicine of metformin (35).

Sulfonylureas

Sulfonylureas (SUs) were introduced in the 1950s. SUs bind to the ATP-sensitive potassium channels of pancreatic β-cells that close in response to elevated cytosolic ATP/ADP concentrations. The potassium channels are composed of a Kir6.2 pore and SUR subunits. One of these subunits is the main target for the SUs and regulates the open and closed statuses of the Kir 6.2 pore based on ATP concentrations. Closure leads to local membrane depolarization and the opening of adjacent voltage-gated L-type calcium channels and results in increasing in cytosolic calcium, which stimulates exocytosis of insulin granules and eventually insulin releases to reduce blood glucose (22,29,36). Submaximal doses of SUs usually reduce HbA1c by 1-2% (22).

Some patients experience failure of SU treatment. This reduced response is related to SNPs in the genes KCNJ11 and ABCC8 that encode Kir6.2 and SUR1 subunits of potassium channel, respectively and also to the metabolizing enzyme Cytochrome P450 2C9 (CYP2C9) (29).

Two separate variants E23K (KCNJ11) and S1369A (ABCC8) have controversially shown associations with T2DM risk and sulfonylurea efficacy (37).

SUs are mainly metabolized by CYP2C9 and T2DM patients with loss of function variants of CYP2C9 having a better glycemic response than those carrying wild-type allele (4).

Other genes have also been associated with response to SUs. Transcription factor 7-like 2 (TCF7L2) variants are associated with reduced efficacy of SUs and also T2DM risk through reduced β-cell function (29).

Nevertheless, there are inconsistent results regarding the development of personalized sulphonylurea medicine for the T2DM management (38).

Meglitinides

Meglitinides were introduced in the late 1990s. Similar to SUs, this anti-diabetic drug class stimulates insulin secretion and usually result into less decrease in HbA1c than SUs (22).

Similar to the Sulfonylureas, the meglitinides act on the potassium channel too, but at a distinct binding site, to stimulate depolarization and insulin secretion as well as on voltage-gated calcium channels.

Inter-individual variability in response to this drug class is associated with single nucleotide polymorphism in the transporters SLCO1B1, OATP1B1, CYP2C9 , CYP2C8 and CYP3A4 (29).

DPP4 inhibitors/GLP-1 analogs

This class of anti-diabetic medications includes dipeptidylpeptidase-4 (DPP4) inhibitors (gliptins) and GLP-1 analogs. DPP4 inhibitors were introduced from

2007. They increase the "incretin effect" by increasing the blood level of the main incretin hormone, glucagon-like peptide-1 (GLP-1), in order to induce insulin secretion. GLP-1 analogs exert their action as incretin mimetics (22). These medications induce incretin signaling pathway and stimulate insulin secretion, prevent glucagon secretion, and decrease gastric emptying and appetite (39,40).

CTRB1 and CTRB2 genes were related to this group of agents, and both encode the digestive enzyme chymotrypsin, as an important regulator of the incretin pathway (41).

SGLT-2 inhibitors

Sodium-glucose transporters (SGLT) located in the renal tubules reabsorbed 99% of the filtered glucose during renal filtration. The main subgroup of these transporters in the renal tubules is type 2; accordingly, SGLT-2 inhibitors reduce hyperglycemia through glucose elimination via urine (26).

A loss of function mutation in SLC5A2 gene, which encodes SGLT2 might remove glucose in an insulin-independent mode via glucosuria and decrease uptake of glucose in the tubuli, thus protecting against hyperglycemia via elevated glucose excretion in the kidney (42). However, there is no pharmacogenetics study about treatment efficacy of SGLT-2 inhibitors at the present time.

Thiazolidinediones

Thiazolidinediones (TZDs) are a class of anti-diabetic drugs that act as insulin sensitizers increasing insulin-dependent glucose. They act essentially through PPAR-γ whose activation leads to expression of genes involved in the insulin signaling pathway. This class of drug ultimately improves insulin sensitivity in diabetic patients. TZDs have the ability to reduce hemoglobin A1c by approximately 0.5-1.4% (22,26,30).

Single nucleotide polymorphisms in the liver drug metabolizing enzyme genes such as CYP2C8, CYP2C9, GSTT1, GSTM1, and ADIPOQ are related to the behavior of TZDs (28,30).

Lipid lowering agent pharmacogenetics and risk of T2DM

In a new meta-analysis study, the association of genetic variants with the risk of type 2 diabetes have been confirmed in or near in NPC1L1, HMGCR, PCSK9, ABCG5/G8, LDLR which encode molecular targets of lipid-lowering therapy. These data provide new insight into the adverse effect of LDL-c-lowering therapy (43).

Table 1. Anti-diabetic drugs and their action and associated genes in drug efficacy and toxicity (4,26,27,29,30,44)

Drug	Drug examples	Gene	Action
Sulphonylureas	Glyburide, Gliclazide, Glipizide, Glimepiride, Tolbutamide	KCNJ11,ABCC8, CYP2C9, TCF7L2	Induce insulin release and secretion
Biguanides	Metformin	SLC22A1, SLC22A2, SLC22A3, SLC47A1, SLC47A2	Reduce gluconeogenesis
DPP4-inhibitors	Sitagliptin, Vildagliptin, Alogliptin,Linagliptin, Saxagliptin	CYP3A4,CYP2C8, TCF7L2	Enhance prandial insulin secretion
Thiazolidineiones	Pioglitazone, Rosiglitazone, Troglitazone, Ciglitazone	PPAR-Y, ADIPOQ1, CYP2C8, CYP2C9, CYP3A4	Decrease plasma free fatty acid levels
SGLT2 inhibitors	Canagliflozin, Dapagliflozin, Empagliflozin	Not yet identified	Prevent reabsorption of filtered glucose
α-glucosidase inhibitors	Acarbose, Miglitol, Voglibose	PPAR-Y, HNF4A, LIPC	Decrease glucose absorption by inhibition of intestinal glucosidase
Glucagon-like peptide-1(GLP-1) receptor agonists	Exenatide, Albiglutide, Dulaglutide, Liraglutide, Lixisenatide	Not yet identified	Enhance prandial insulin secretion
Meglitinides	Repaglinide, Nateglinide	SLCOB1, CYP2C8, CYP3A4, TCF7L2, SLC30A8,IGFBP2, KCNJ11, KCNQ1, UCP2, NAMPT, MDR1, PAX4, NEUROD1, SLCO1B1	Induce insulin secretion

Genetics of T2DM

Implementation of precision medicine in diabetes encounters several challenges. The most important issues are accurate and precise understanding of diabetes. Different studies should be replicated, and information gained from these studies should be interpreted as physiological insight and support to clinical decision making (45).

Investigation of T2D susceptibility genes may be valuable regarding p4 medicine, especially in prediction, prevention and the early treatment of T2DM (46).

Three separate approaches have been applied to the search for the genetic basis of T2DM: linkage studies, investigation of a T2DM candidate gene for T2DM and genome-wide association studies. A susceptibility gene, which has been found through linkage study was TCF7L2, and the association of PPARG and KCNJ11-ABCC8 with T2DM have been found by the candidate approach (47).

Genome-wide association studies (GWAS) by next-generation sequencing bring forward a new opportunity for characterizing specific risk allele of T2DM (disease process) and may help for stratification of interventions. GWAS yielded a significant number of genomic loci linked to T2DM risk that is related to various biological pathways (48). GWAS provided inexpensive disease-informative variants as they can be used for preventive or therapeutic interventions and clinical management. GWAS show a breakthrough in the identification of T2DM-associated loci and a common variant model may exist for the larger fraction of T2DM genetic architecture (49-51). Interestingly, nearly a quarter of GWAS data concern endocrinology diseases (52).

GWAS have introduced more than 150 risk alleles which can be responsible for only about 10% of the variation in type 2 diabetes tendency (53,54). Most of these genes encode intracellular proteins that mediate the secretion of insulin from pancreatic beta cells, but one of these candidate genes encode a cell-surface G-protein-coupled receptor (GPCR): melatonin-receptor gene MTNR1B. Persons with the risk allele of MTNR1B are at increased risk for T2DM through beta cell dysfunction, which causes reduced insulin secretion (48,54).

The advent of GWAS era has confirmed the polygenic nature of T2DM and interestingly brings in a strong role for beta-cell function (insulin secretion) as opposed to insulin resistance in the T2DM pathophysiology (51).

Nearly 26.7 million variants for T2DM association have been analyzed of which 126 variants at four loci (TCF7L2 and ADCY5, CCND2, EML4) were associated with T2D (55).

Because of the polygenic nature of T2DM, larger collections of genetic data will be necessary to discover T2DM related variants in the population, although these associations need to be translated into T2DM pathophysiology (49).

In a recent study from Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial in patients with type 2 diabetes that underwent intensive glycemic therapy, two genetic variants (rs9299870, rs57922 on chromosome 10 and 5 respectively) predict the cardiovascular effects in these patients (56).

On the other hand, different studies have identified genotype- epigenotype interactions at T2DM loci that may predict diabetes risk (57).

Personalized medicine and diabetes mellitus (DM) complications

Type 2 diabetes mellitus encompass microvascular (nephropathy, retinopathy, and neuropathy) and macrovascular complications. Occurrence and progression of diabetes complications are influenced by modifiable risk factors of diabetes, such as high blood pressure and high blood cholesterol levels. Furthermore, these complications may also be influenced by genetic predisposition variant (58).

Many efforts have been made for the better management of diabetes mellitus in the last years. However, most patients with diabetes develop these complications.

After 15 to 2o years diagnosis of DM, about 50%-80% of patients show retinopathy, up to 30% have shown an early stage of nephropathy and about 50% of patients show symptoms of peripheral neuropathy (6).

Each of the pharmacogenetics approaches for glycemic management discussed earlier represents personalized diabetes care not only in blood glucose concentration control but also in diabetes complications.

Mechanistic heterogeneity of diabetic kidney disease (DKD) causes reduced capability to identify risk variants. Some risk variants from APOL1, UMOD genes have been reported, and APOL1 is independent of diabetes status. A well-known GWAS for DKD is related to insertion/deletion (I/D) variant in the gene encoding ACE. Diabetic retinopathy is the other microvascular complication with two candidate genes VEGFA and AKR1B1. Genetic investigation of diabetic neuropathy encounter some restrictions related to small sample size (59).

Severity and pathology of macrovascular

complications such as coronary artery disease (CAD) and ischemic stroke are different, because of comprehensive difference in the pattern of variations which influences the risk of CAD or ischaemic stroke in patients with diabetes and normal individuals (59).

Type 2 diabetes mellitus, a complex disease, which is influenced by modifiable and non-modifiable risk factors (Figure 2). Truly personalized medicine approach (P4 medicine) for the management of T2DM patients is needed for better understanding of the onset and course of T2DM, pathophysiological mechanism of T2DM, prevention of T2DM complication and finally treatment planning (1,7,12,45).

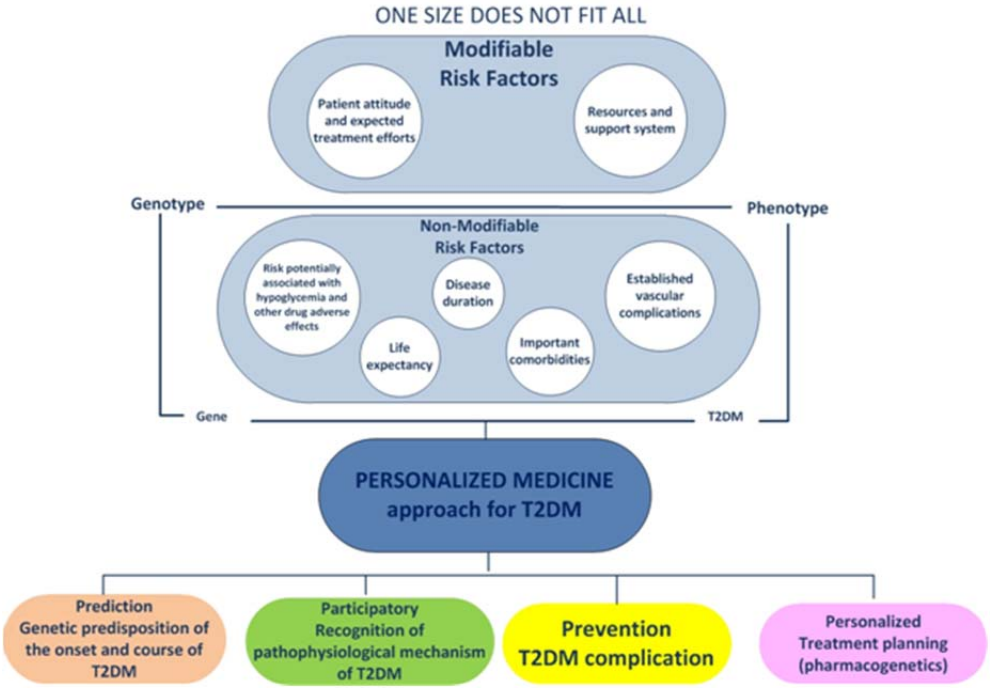

Figure 2. Overview of the pathophysiologic mechanism of T2DM

Conclusion

Although the evidence-based guidelines, as the first revolution in diabetes care, have been notably improved the quality of diabetes management, we have to use the lens of personalized medicine as a second revolution in diabetes care.

In spite of newly recognized diabetes molecular pathways, there is a large gap between molecular knowledge of diabetes and using it in the clinic or at the bedside. Evidence-based medicine is going to narrow this gap by applying the results of meta-analyses in clinical practice. However, there are large variations in symptoms, manifestations of disease and genetic variations related to drug efficacy and its adverse reactions, i.e. "Pharmacogenetics aspects" of the diseases. Consequently, we have encountered some difficulties in translating the results of meta-analyses into the practical guidelines, since the meta-analyses cannot reflect the genetic variations, which should be in the concept of any study.

Precision medicine evidence based is growing, but we must resolve the problem of big data and its translation to an actionable clinical decision system.

The ultimate goal of personalized management of diabetes is to provide a user-friendly decision support tool by applying “Omics data” in order to implement a cost-effective and best-tolerated treatment strategy based on patient’s genetic architecture. In the very near future, personalized medicine, which holds tremendous potential, will play its greater role at the bedside.

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