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Review

A Novel Comprehensive Program Combining Optimal Medical Treatment with Lifestyle Modification for Type 2 Diabetes

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ABSTRACT: There are more and more individuals with type 2 diabetes (T2D) in the globe. It's a huge burden of public health and a great challenge in clinical due to a high linkage with atherosclerosis, cardiovascular disease (CVD), stroke, and cancer. However, little is known about a comprehensive program of management and self-management of T2D. This article introduces briefly the current status in T2D and an updated classical standardized comprehensive program which combines optimal medical treatment (OMT) (the glucagon-like peptide-1 receptor agonists, the sodium-glucose cotransporter 2 inhibitors, and the ultralong-acting, once-daily basal insulin) with lifestyle modification, that is, intervention of RT-ABCDEFG (iRT-ABCDEFG) for control and prevention of T2D, and discusses its advantages and prospects. As an effective comprehensive program and strategy for interventions of diabetes, this program can be used as a reversible, right, and routine treatment. Several pivotal goals including less major adverse cardiocerebrovascular events (MACCE) and diabetic complications, less medical costs, longer life expectancy, lower morbidity and mortality, and higher quality of life, will be realized by consistently practicing this program due to early diagnosis, OMT, and lifestyle modification for overall prevention. All in all, since T2D highly links to CVD and cancer, as well as other MACCE, this novel iRT-ABCDEFG program is very helpful in comprehensive management and self-management of T2D and worth recommending for further application and health care of T2D due to better clinical efficacy and cost-effective relationship.

Keywords: iRT-ABCDEFG; Lifestyle; Prevention; Treatment; Type 2 diabetes

1. Introduction

Type 2 diabetes (T2D) is one of major non-communicable diseases (mNCDs) that requires lifelong treatments and management of high glycemic level. More than 400 million adults worldwide suffer from diabetes [1]. Obesity, physical inactivity, and unhealthy diet are major risk factors in adults diabetes [2], and racial & ethnic groups, maternal obesity have also led to a relative increase in T2D. In fact, the incidences of both type 1 and T2D increase significantly, particularly among minority racial and ethnic groups [3]. Although mortality and fatal outcomes declined in individuals with T2D in some developed countries [4], for example, in Sweden from 1998 through 2014, it's still a big challenge and a heavy burden in developing countries.

Since high-quality care for individuals with T2D could decrease unnecessary emergency visits [5], for example, urine glucose screening within community and schools may help to detect early asymptomatic T2D [6], and individuals with T2D need to exercise more often (at least meeting physical activity guidelines) for reduction of mortality [7]. However, considerable proportion of T2D patients in some Asian countries and regions, for example, South Korea, were not adequately managed and lack of high-quality care due to no reliable comprehensive program [8]. In addition, a large-scale international study showed that subjects with T2D frequently have depression and psychological and psychiatric problems [9]. Thus, there is arising evidence for better management of T2D, since it is an independent predictor of revascularization and long-term mortality [10]. Based on these features of T2D (high prevalence, high risk

for adverse clinical outcomes, and high burden of public health) as well as lack of a high quality program for management of T2D, we wrote this review and aim to conduct a novel comprehensive program combining optimal medical treatment (OMT) with lifestyle modification for T2D.

2. Current Status and Main Treatment of T2D

T2D is one of the most prevalent diseases and one of the leading causes of morbidity and mortality worldwide. Currently, over 10.5% of the adult population has been diagnosed with T2D, and almost 12% of total health expenditure is spent exclusively on T2D management globally. And there is increasing incidence of T2D among youth since the incidence of overweight and obesity among children has increased dramatically in recent decades. However, most youth with T2D do not achieve optimal glycemic control, and are at high risk for later cardiometabolic health complications, which include microvascular complications (nephropathy, neuropathy, and retinopathy) and macrovascular complications, such as acute myocardial infarction (AMI), chronic heart failure (CHF), and strokes.

Currently, treatment of T2D focuses on glucose-lowering medication and non-pharmacological treatment. (Table 1) The former includes oral hypoglycemic agents, insulin pump or injection therapy; The later includes surgical treatment, for example, bariatric surgery for markedly obese individuals with T2D, and modification of unhealthy lifestyle. Newer anti-diabetic drugs such as the sodium-glucose cotransporter 2 (SGLT2) inhibitors (SGLT-2i) and the glucagon-like peptide-1 receptor (GLP-1 R) agonists (GLP-1 RA) can reduce the risk of both microvascular complications and macrovascular disease in patients with T2D. However, most patients with T2D have not achieved optimal glycemic control with mono-therapies. Moreover, some treatments may have side-effects [11]. Although current guidelines for T2D are suitable for clinical doctors to use, it isn't for individuals' self-management of T2D. Of course, there is still a need for self-control of glucose levels in a new era of personnel medicine.

Since current main treatment of T2D remains a challenging issue, and therapeutic goals are often not achieved. Herein, we proposed the iRT-ABCDEFG program combining OMT with lifestyle modification as a novel comprehensive strategy for better T2D management.

Table 1. Current main treatment of T2D.

T2D Treatment	Traditional Agents	Newer Agents	Insulin Therapy	Non-Pharmacological Interventions (NPI)	Molecular Strategies
Oral anti-diabetic drugs (OADs)	**Metformin** **Sulfonylureas (SUs)** **Newer generation SUs** e.g., gliclazide modified release (MR) **Traditional medicinal herbs** as complementary or alternative medicine (CAM) & adjunctive therapeutic strategies e.g., cinnamon, saffron, ginger, jujube, turmeric, and barberry	**Sodium-glucose cotransporter type 2 inhibitors (SGLT2i) *** -- new class of oral antidiabetic agents e.g., dapagliflozin, canagliflozin, empagliflozin, ertugliflozin, and bexagliflozin (5th) **Glucagon-like 1 peptide receptor agonists (GLP-1RA) **** (Food and Drug Administration-approved, oral or injectable) e.g., **monotherapy** Liraglutide Semaglutide **Dual (GLP-1/GIP)/triple agonists** tirzepatide, cagrilintide 2.4 mg/semaglutide 2.4 mg, survodutide, mazdutide, retatrutide (Common adverse events: vomiting, nausea and diarrhoea) **Non-steroidal mineralocorticoid receptor antagonist (nsMRAs) #** e.g., finerenone, esaxerenone and apararenone	**Insulin injection** **oral insulin delivery** (overcoming gastrointestinal barriers, including enzymatic degradation, low permeability, food interactions, low bioavailability, and long-term safety concerns) **Microfluidic platforms** for oral, intraperitoneal, and inhalation-based delivery of insulin (Microfluidic technologies and devices)	**Bariatric surgery** or **metabolic surgery** for weight loss **Nutrient-gut microbiota (GM) interactions** as a strategy to alleviate T2D **Lifestyle interventions** **Diet therapy or functional foods as CAM Treatment** e.g., adzuki beans in the diet as a strategy for preventing and managing T2D pomegranate consumption **Other NPIs** e.g., increasing physical activity	**Gene-editing strategies** e.g., CRISPR/Cas9 **RNA-based therapeutics** e.g., Microribonucleic acids (miRNAs) as agents and as druggable targets. (e.g., downregulation of miR-7) **Mitochondrial Replacement Therapies (MRT) techniques ##** **Others** Reserving insulin-producing β-cells and hence restoring insulin production By the generation of exogenous β-cells from stem cells and single-cell studies

Notes: Please follow guideline-directed medical therapies of T2D and its complications. ***** A more significant weight loss and blood pressure reduction and a lower risk of hypoglycaemia. ****** Better cardio-renal benefits, long-term efficacy and safety as well as cost-effectiveness. **#** The nsMRAs are now an important component of recommended treatment for chronic kidney disease (CKD) associated with T2D. **##** Need a careful balance between innovation and safety. GIP: glucose-dependent insulinotropic polypeptide; GLP-1: glucagon-like peptide-1.

3. An Updated Standardized Comprehensive Program

How can an individual control and prevent T2D with a simple and effective method? We strongly recommend an updated classical standardized comprehensive iRT-ABCDEFG program (Figure 1) for clinical professional management and family health care of T2D. Here, G means goals; F means follow-up; E means examination; D means disease & risk factors control; C means changing unhealthy "environment-sleep-emotion-exercise-diet" intervention [E(e)SEEDi] lifestyle & Chinese medicine or control the source of infection & cutting genetic or spreading pathways during the COVID-19 pandemic; B means biohazard control; And A means antagonistic treatment, such as optimal anti-diabetic agents, which include traditional agents (for example, metformin and others), and novel chemical agents, such as [GLP-1 RA, SGLT-2i, the ultralong-acting, once-daily basal insulin, and others].

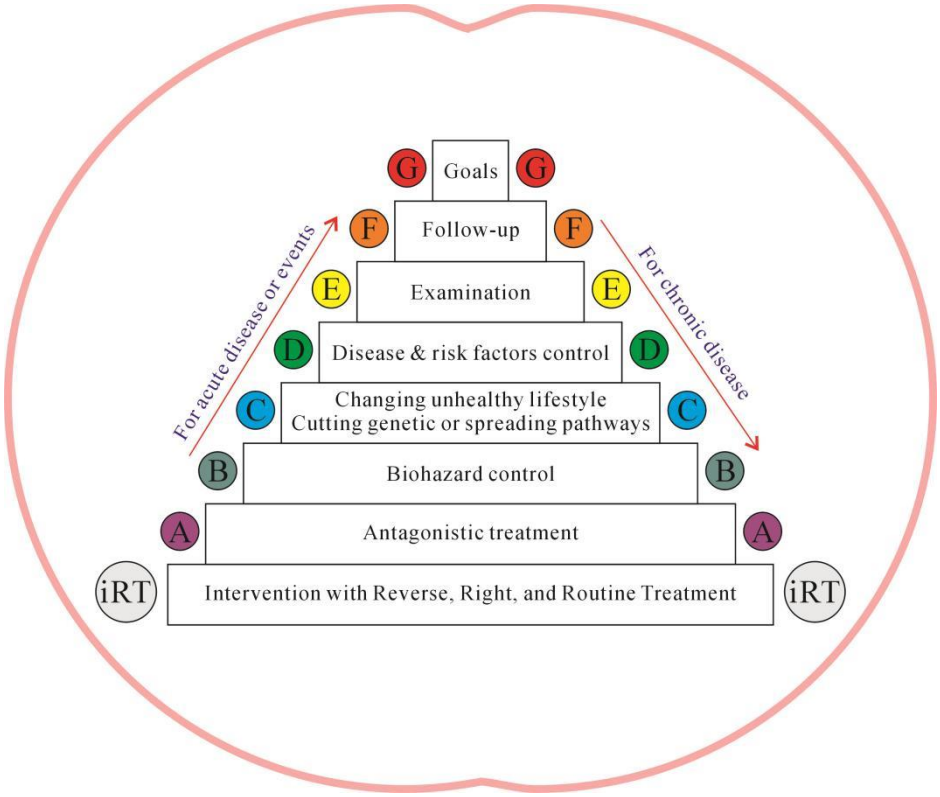

Figure 1. The iRT-ABCDEFG program for managing type-2 diabetes (T2D).

According to this figure, it's easy to understand that this comprehensive program is very helpful to control and prevent T2D and reach several pivotal goals after consistently practice, which include less major adverse cardiocerebrovascular events (MACCE) and diabetic complications, less medical costs, longer life expectancy, lower morbidity and mortality, and higher quality of life, due to early diagnosis, OMT, and healthy E(e)SEEDi lifestyle for overall prevention. Herein, this iRT-ABCDEFG program is worthy of recommending for clinical professional management and health care of T2D due to better cost-effectiveness. However, it needs to confirm by long-term follow-up and clinical trials. In fact, it is suitable for not only acute diseases or events, such as acute myocardial infarction (AMI), stroke, and COVID-19 infection, but also chronic diseases, such as C-type hypertension (CtH), chronic heart failure (CHF), chronic kidney disease (CKD), neurodegenarative diseases (dementia or Alzheimer's disease and Parkinson's disease), and cancer as well as the cardiovascular, diabetes, and cancer (CDC) strips.

As a novel strategy for Intervention of diabetes, this program can be used as a Reverse, Right, and Routine Treatment in clinical practice. The detailed tips are as follows (Table 1).

This iRT-ABCDEFG program is very suitable for not only control of risk factors and cardiovascular disease (CVD), e.g., hypertension [12], AMI [13], CHF [14], and arrhythmogenic right ventricular cardiomyopathy [15] as well as cancer [16] and major virus-communicable diseases [17], but also T2D. Firstly, good goals help to work better. Moreover, as an updated classical, individualized, and concise "guideline", if treated as "a law" in clinical practice, the vital goals which include less MACCE and diabetic complications, less medical costs, longer life expectancy, lower morbidity and mortality, and higher quality of life, will be realized by consistently practicing this iRT-ABCDEFG program due to early diagnosis, OMT, and overall prevention by healthy E(e)SEEDi lifestyle.

On the one hand, follow-up of both doctors with patients and patients with doctors will improve outcomes. For example, follow-up found that intensive glucose control reduces MACCE [18], but bariatric surgery plus intensive medical therapy is more effective for control hyperglycemia than intensive medical therapy alone [19]. Individuals' comprehensive or targeted examinations or population-based large-scale screening (e.g., urinary glucose screening) will help the early diagnosis of both symptomatic and asymptomatic T2D [6,20]. For example, there are only 10% undiagnosed cases of diabetes in the United States due to large-scale screening, and diagnoses by the criteria of elevated levels of fasting glucose (≥7.0 mmol/L) and hemoglobin A1c (HbA1c, ≥6.5%) [21].

Since postpartum follow-up and screening of oral glucose tolerance test (OGTT) during the delivery hospitalization is helpful to control maternal T2D, follow-up of women after delivery and scheduled screening for preventing T2D is very important for against this public health issue. Whatever, early examination and screening will help the management of T2D and decreasing its complications. Some serum biomarkers are helpful to determine its severity and complications, such as fibroblast growth factor 21 (FGF21) [22], the receptor for advanced glycation end products (RAGE) [23], and salusin-α and salusin-β levels [24]. In addition, albuminuria level is also associated with higher risk of MACCE (AMI, stroke) in patients with T2D [25].

On the other hand, this program helps to control T2D-related complications and major risk factors by cutting genetic pathways and changing unhealthy lifestyles, which can also decrease diabetic gene mutation. Studies have already shown that intensive lifestyle intervention in patients with T2D is beneficial to control individuals' glycemic levels [26], e.g., intensive body weight management [2]. Moreover, healthy lifestyle included five core elements—"environment-sleep-emotion-exercise-diet" intervention [E(e)SEEDi] [27,28] may achieve better goals in control and prevention of T2D (Table 2) [29–43].

Table 2. The iRT-ABCDEFG program as a standardized comprehensive program for T2D.

iRT-ABCDEFG	Tips
G	**Goals** are less MACCE and diabetic complications, less medical costs, longer life expectancy, lower morbidity and mortality, and higher quality of life.
F	**Follow-up** with registered subjects or patients, especially populations with family history, IGT, and an unhealthy lifestyle for primary and secondary prevention, tracking outcome and evaluating effects of intensive medical therapy (oral drugs or insulin injection) and surgery. It's very important for a population-based study.
E	**Examination** for early diagnosis, treatment, and prevention, which includes large-scale screening and regular comprehensive or targeted physical examinations, such as biomarkers (fasting blood-glucose, postprandial blood glucose, hemoglobin Alc, and others: FGF21, lipoprotein(a), microalbuminuria, RAGE, salusin-α and salusin-β), oral glucose tolerance test, β cell function, genetic variants (e.g., nitric oxide synthase 1 adaptor protein, FOXO1 gene), ultrasonography, histopathological analysis, coronary angiography, CT angiography & MRI. Risk stratification following these examinations and related scoring will improve treatment and clinical outcomes.
D	**Diseases and risk factor control**, which includes prediabetes state or impaired glucose tolerance, hypertension, dyslipidemia, chronic infection, and diabetic complications (e.g., retinopathy or chronic kidney disease, hypoglycemia, peripheral neuropathy, diabetic ketoacidosis and other CVDs), obesity, physical inactivity, and heavy drinking or smoking.
C	**Change unhealthy E(e)SEEDi lifestyle** with SEEDi$^{1.0–3.0}$ technologies, such as not staying up late, being physically active, no smoking and drinking; **Chinese medicine** is a good choice; **Controlling the source of infection** and **the spread of pathways** during the pandemic are vital strategies if accompanied by acute infectious diseases (e.g., COVID-19); And **Cutting off the genetic pathways** by RNAi, gene knockout or CRISP/Cas9 gene editing after an ethical approval and patients consent due to a genetic predisposition to diabetes.
B	**Biohazard control**, which includes abnormal symptoms and physiological indexes, HbA1c level of bio-markers, family history, intensive weight management for obesity, and control of diabetic complications. Monitoring or self-monitoring of blood glucose levels is important and necessary.
A	**Antagonistic treatment,** which includes oral hypoglycemic agents (such as GLPR agonists, SGLT2 inhibitors), insulin monotherapy, statin-based treatment, bariatric surgery, guidelines and other related methods.
iRT	intervention with these strategies as Routine, Right & Reversible Treatment.

Notes: SEEDi$^{1.0–3.0}$ technologies were developed based on core healthy elements; that is, sleep-emotion-exercise-diet (SEED) intervention (SEEDi). When E(e)SEED-BasED healthy lifestyle included external and internal environment combines with RT-ABCDEF and Grade 210 prevention, it's 3.0 version of SEEDi (SEEDi$^{3.0}$) or General Formula (Health & Longevity equality) for major non-communicable diseases (mNCDs). GLPR agonists: glucagon-like peptide-1 receptor agonists; SGLT2 inhibitors: sodium-glucose cotransporter 2 inhibitors.

As we already known, CVD and T2D are more common in some populations (such as taxi drivers) due to unhealthy lifestyle [44]. However, healthy lifestyle is associated with a lower risk of CVD incidence and mortality among adults with T2D [45], it plays a key role in risk factor management for primary prevention of CVD [46]. In fact, lifestyle modification can reduce risk factors in both CVD and T2D [47]. However, current lifestyle modification is still low among US adults with chronic conditions [48]. Therefore, healthy E(e)SEEDi lifestyle should be recommended to all individuals in the globe.

Previous studies showed that exercises were associated with significantly lower HbA1c and fasting blood glucose [49], and plant-based diets which include legumes, whole grains, vegetables, fruits, nuts, and seeds, not only reduce the risk of T2D but also help to prevent T2D [50]. However, there are no significant difference in MACCE from n-3 fatty acid supplementation among T2D patients without CVD [51], Vitamin D_3 supplementation did not result in a significantly lower risk of T2D [52]. Without a doubt, individualized biohazard control and antagonistic treatment are necessary according to "5P" medical model [53], because T2D can easily result in injury of organs and a series of complications without long-term optimal glycemic control, for example, erectile dysfunction, lipoprotein (a) and microalbuminuria are predictors of vascular complications [54–56]. The EUCLID Trial showed that every 1% increase in HbA_{1c} was associated with a 14.2% increased relative risk for MACCE in patients with diabetes and peripheral artery disease [57]. There are less costs and better quality of life among patients with individualized glycemic control than uniform intensive control (HbA1c level < 7%) [58].

On antidiabetic medical treatment, clinical studies already showed that the GLPR agonists, semaglutide [59] and liraglutide [60–62] the SGLT2 inhibitors [63], canagliflozin [64,65] and empagliflozin [66–68], and an ultralong-acting, once-daily basal insulin degludec [69], are not only helpful to glycemic control but also reduce MACCE including cardiovascular death or hospitalization for heart failure (HHH) in subjects with T2D and/or slower progression of diabetic chronic kidney disease (CKD). Since both were not associated with high rates of venous thromboembolism [70], the SGLT2 inhibitors and the GLPR agonists had already been recommended by the 2019 guidelines of American Diabetes Association (ADA) [71]. It can be said that 2 new classes of antihyperglycemic agents [72], the GLPR agonists and the SGLT2 inhibitors, have indeed led to a paradigm shift of T2D treatment. However, a study found that, a selective SGLT2 inhibitor dapagliflozin [73], not result in a higher or lower rate of MACCE, but in a lower rate of cardiovascular death or HHH.

In addition, the nonsteroidal, selective mineralocorticoid receptor antagonist (MRA) finerenone can reduce the risk of new-onset atrial fibrillation or flutter (AF/AFL) in patients with T2D and CKD [74]. Of course, there is still improper use of aspirin for primary and secondary prevention of CVD in T2D [75]. According to its cost and safety profile, metformin should be the first line drug therapy for patients with newly diagnosed T2D [76]. Due to cardiovascular benefit and lower achieved LDL-C levels associated with lower risk of MACCE [77], statin therapy should be recommended for primary prevention in the elderly with or without T2D [78]. In fact, it is also easy to understand the treatment of T2D and its complications from other systematic reviews, including relatively complete existing drugs, therapeutic effects, adverse events, and other aspects. Therefore, we will not list and summarize here.

4. Advantages of the iRT-ABCDEFG Program

Since T2D is as dangerous as coronary heart disease and associates with higher MACCE, which include cardiovascular and non-cardiovascular hospitalizations, AMI, CHF, ischemic stroke/TIA recurrence, and death [79], abnormal glycemic levels link to high mortality and morbidity. For example, on the one hand, maternal T2D highly links to arterial stiffness, cardiac hypertrophy, and congenital heart defects; On the other hand, there is increasing T2D in offspring in late adult life due to maternal gestational hypertension. Thus, we think that there are obvious advantages of this iRT-ABCDEFG for T2D, which will help to realize the European Society of Cardiology's ambitious mission "to reduce the burden of CVD" in countries worldwide [80].

Most cases of new onset T1D in China occurred among adults [81], this iRT-ABCDEFG program is suitable for not only T2D but also T1D because it can help to decrease and delay onset of T1D by healthy E(e)SEEDi lifestyle and cutting a genetic pathway in the early stage of one's lifetime due to control of maternal risks. Thus, this iRT-ABCDEFG program is worthy of conducting in the globe. In addition, since T2D is surprisingly closely linked to AMI, CHF, and stroke, diabetic chronic kidney disease (CKD), maximum effort must be made to control the prevalence of T2D so as to halt CVD and its costs increasing. Since policy initiatives can help controlling increases in health care spending [82], it's time for not only *Health in All Policies* but also *Health in All Laws* [16,83].

With the further studies on mechanisms and the continuing development of new drugs and novel technologies for T2D, more precise and effective management or self-management of T2D with this iRT-ABCDEFG program is possible due to the role of structure-editing on unhealthy lifestyle [84], and long-term trends in mortality and the incidence of MACCE will also decline. For example, a clinical trial confirmed that oral insulin 338 can safely improve glycaemic control in insulin-naive patients with T2D, although it isn't in place of subcutaneous insulin glargine yet due to being not commercially viable at current stage [85].

In short, since some cardiovascular metabolic factors of T2D, such as obesity, physical inactivity, obstructive sleep apnea (OSA), hypertension, and other modifiable unhealthy E(e)SEEDi lifestyle-related factors, may induce MACCE (AF, AMI, CHF, Stroke) and reduce health span and life span [86,87], control and prevention of these risk factors according to this iRT-ABCDEFG program will get more clinical benefit and improve cardiovascular outcomes. The SGLT2 inhibitors and GLP-1 receptor agonists, the newer classes of antihyperglycemic agents with the cardiorenal protective effects [88], will add distinctly clinical benefit. The MRA finerenone also reduces the composite kidney and cardiovascular outcomes [89].

5. Future Perspective

It can be easily found that this comprehensive program will help to translate new technologies and research into clinical practice and reverse T2D due to strengthening prevention and management or self-management as well as personalized services. It will meet not only Healthy China 2030 Plan but also updated the National Health Service (NHS) Long Term Plan in the UK [90]. In short, this program can help to achieve global health goals.

In fact, this program has already been used for CVD and cancer in daily clinical practice, but there are more detailed recommendations for on changing an unhealthy lifestyle to manage T2D (Table 3). If there was a national registered centre for T2D, similar to those for major communicable diseases like SARS and COVID-19 [17,91], more satisfactory results could be achieved through reliable national clinical trials using this innovative comprehensive program. This program combines anti-diabetic agents, insulin use, metabolic surgery, mental health screenings, and the healthy E(e)SEEDi lifestyle [27,92,93], which includes a plant-based diet. This approach could lead to better control of population-level HbA1c and cardiovascular risk among individuals with T2D.

Table 3. The effects of healthy or unhealthy E(e)SEEDi lifestyle on T2D: Evidences from PubMed literature.

E(e)SEEDi (Healthy or Unhealthy)	**Linkage to T2D Risk (Lower or Increase)**
Environment (external or self-internal)	Clinical studies confirmed that long-term exposure to air pollution links to the increased risk of both CVD and T2D [29–33]. And increased transportation noise and e-noise exposures are associated with a greater risk of T2D [34–36]. Early growth status (short length and/or thinness at birth and during infancy) also links to T2D [37].
Sleep	Sleep breathing disorders (severe obstructive sleep apnea, OSA) may add the risk of T2D [38].
Emotion	Work-related psychosocial stress may increase the risk of T2D [39].
Exercise	Aerobic physical activity is associated with reduced risk of T2D and the higher levels of muscle-strengthening activities, the lower risk of T2D [40]. For example, leisure-time running is associated with a lower risk of developing T2D in adults [41].
Diet	Smoking (nicotine intake) increases the risk of T2D, but there is a protective role of habitual intake of filtered coffee on T2D development [42,43].

Notes: If individuals can keep healthy E(e)SEEDi lifestyle, they will basically get away from T2D or at least lower the risk of T2D.

With a better understanding in the pathophysiological mechanisms at the molecular level and the discovery of new targets for metabolism [94,95], the implications for existing guidelines and therapeutic options, as well combination with this iRT-ABCDEFG program and effective lifestyle interventions for T2D, for example, a precision dietary management and scientific dietary recommendations with respect to carbohydrate, fat and dietary fibre, and increases in physical activity and fitness, calorie restriction and weight loss [96,97], these individuals will improve greatly glycaemic control and better prevent its complications [98], such as CVD and neurodegenarative diseases (Alzheimer's disease and Parkinson's disease) [99]. In addition, the prevalence of both depression and thyroid abnormalities is high among individuals with T2D [100,101]. and coronary plaques [102], abnormal gene expression and serum biomarker levels in these patients mean higher risk and adverse clinical outcomes [103–105], hence, we should control and prevent these risk factors so as to reduce cardiovascular mortality.

Theoretically, this iRT-ABCDEFG program is more plausible for better management and self-management of T2D due to truly individualized glycaemic goals. Early detection of ischemic heart disease and unrecognized CHF is beneficial for individuals with T2D. Treatment with statins and SGLT2 inhibitors can safely improve lipid levels and endothelial function, ultimately lowering the risk of MACCE [106]. Additionally, a biomarker score can be used to stratify the risk of CHF in individuals with T2D and pre-diabetes [107]. Healthy E(e)SEEDi lifestyle may help to reduce these risks and improve clinical outcomes [108]. In addition, clinical trials already confirmed benefits of selective nonsteroidal MRA eplerenone [109] and finerenone [110] in CHF prevention and cardiovascular outcomes improvement. Obviously, a combination of these strategies in this novel comprehensive program is helpful to healthcare of individuals with T2D. Of course, both drug and non-drug management of T2D require more solid evidence-based studies [111].

Since there are more cardiovascular benefits in SGLT2 inhibitors, such as dapagliflozin [112], and new animal models and clinical trials had already confirmed the glucose-lowering potential of glucokinase activators [113], and there are more and better choices for T2D treatment, but we should pay more attention to both safety and efficacy of these novel hypoglycaemic drugs [114]. Because T2D links to significant abnormalities in cardiocerebrovascular system [115], such as atherosclerotic CVD, diabetic cardiomyopathy, CHF, stroke, CKD, peripheral neuropathy [116], our program may have a role of risk-reduction of MACCE and improvement of clinical outcomes. Herein, this program can be adopted as "a concise guideline" in clinical practice due to OMT and healthy E(e)SEEDi lifestyle.

Both T2D (diagnosed and undiagnosed) and IGT are important CVD risk factors [117] and have higher risk of coronary stenosis and coronary atherosclerotic plaques burden [118]. When there is fragmented QRS, it may predict complex VAs and the risk of sudden cardiac death [119], and LVDD is common [120] in T2D patients, it may also be detected by 3D speckle tracking echocardiography [121]. However, current SGLT2-inhibition remains to be at an underused status in these HF-population [122]. A combination of agents high-intensity statins (rosuvastatin) and more often with ezetimibe [123] and intensifying lifestyle measures is needed for stricter LDL-C and non-HDL-C targets.

Because good clinical investigations or programs could inform future diagnostic and therapeutic strategies, and enhance the understanding of a disease, just like myocardial infarction with nonobstructive coronary arteries (MINOCA) [124] and this iRT-ABCDEFG program. When combined with novel tools [125], new agents [126], fresh preventive and interventional strategies [127,128], it will help us to get better effects on management or self-management of T2D. However, "advances in science are not linear, they are zigzag" [129]. Thus, we should keep enough patience and confidence from papers publication to practical application and try to expand related clinical coverage.

During the pandemic and post-COVID-19 era [130], both GLP-1 receptor agonists and SGLT2 inhibitors, when combined with the healthy E(e)SEEDi lifestyle, are effective in preventing related complications in T2D, such as CHF, CKD, and AF/AFL-reduction benefit. These medications have direct and favorable effects on protecting the heart and kidneys [131–134]. However, it should be noted that SGLT2 inhibitors do not have significant effects on ischemic events caused by atherosclerotic CVD in T2D [135]. With the development of new drug delivery systems [136–138] and technologies [139,140], there is potential for these medications to be even more effective in treating T2D and its complications.

As part of a healthy lifestyle, certain diets have been found to be beneficial in managing T2D. For example, the Mediterranean diet, which is rich in olive oil [141], and avoids animal fats and refined carbohydrates can be helpful. Additionally, incorporating whole grains [142], substituting yogurt or reduced-fat milk for cheese [143], and supplementing with folate [144] can also be beneficial. Consuming dietary fibers (DFs), particularly soluble fibers (SFs), from fruits [145] and drinking green tea daily [146] can also have a positive impact. Moderate alcohol consumption [147], particularly wine, with meals [148] and increased consumption of caffeinated coffee [149] have also been linked to a lower risk of T2D. However, it is important to note that long-term consumption of artificially sweetened beverages (ASB), sugar-sweetened beverages (SSB), and total sweetened beverages (TSB) (a combination of ASB and SSB) have been associated with an increased risk of T2D [150].

In addition, low birth weight and childhood obesity were associated with higher risk of adult T2D [151]. No association of mushroom consumption with biomarkers and risks of CVD and T2D in US adults [152], and not support an inverse association of yogurt consumption or other dairy consumption with T2D risk in black women [153], no overall association between moderate egg consumption and risk of T2D [154], But higher selenium concentration [155], an adequate vitamin D status (around 50 nmol/L) and avoiding deficiency may help to prevent CVD complications among patients with T2D [156].

New targets link to novel therapeutic strategies of T2D and its complications (CKD), such as the CCL25-CCR9 axis [157], the IL-8-CXCR1/2 axis [158], IL-6/glucagon [159], Circulating ApoJ [160], hydroxysteroid 17-beta dehydrogenase 6 (HSD17B6) [161], and the gut microbiota [162], and modification of lifestyles may reduce the risk of

T2D, such as high adherence to a mainly plant-based diet [163], improving cardiorespiratory fitness [164], and the combination of antidiabetic agents and lifestyle [165]. In addition, circulating miRNAs, particularly miR-486, miR-146b and miR-15b, are helpful in predicting the future risk of T2D [166].

Since cases with T2D is easy to suffer from diabetic dyslipidaemia [167] and dementia [168], healthy lifestyle plays a vital role on lowering these risks. A series of studies showed that healthy lifestyles highly link to lower T2D risk, for example, foods of whole grains[169], fruits, and dairy [170], a more plant-based and less animal-based diet [171], moderate wine consumption [172] among overweight women, but lower levels of cognitive function [173], sedentary behaviors (total sitting and TV viewing) [174], foods of red meat, processed meat, and sugar-sweetened beverages [170], and novel inflammatory markers (EN-RAGE, IL17, and IL13) [175] link to high T2D risk. In fact, changes in body shape after puberty [176], excess body weight [177], and visceral adipose tissue [178] may serve as an evaluating tool for prediction of T2D incidence. In a word, with the development of new pharmacotherapeutic approaches, novel therapeutic targets, and fresh lifestyle medicine, the up-to-date personalized therapeutic plan and program for T2D will be great helpful in the control and prevention of T2D.

6. Conclusions and Recommendations

This iRT-ABCDEFG program combining OMT and healthy E(e)SEEDi lifestyle for T2D is very suitable for healthcare among clinical doctors, patients, and healthy individuals. This program is helpful to access clinical vital goals, which include less MACCE and diabetic complications, less medical costs, longer life expectancy, lower morbidity and mortality, and higher quality of life due to early diagnosis, OMT, and overall prevention by healthy E(e)SEEDi lifestyle. Moreover, this program is not only effective but also not complicated, and easy to perform in primary care centers. In addition, training the professional members and individuals to carry out this program is so easy. In fact, this program can also be developed as a mobile APP for wide use among T2D individuals and general population. Herein, we highly recommend this iRT-ABCDEFG program due to a good expected cost-effective relationship and clinical outcomes, since T2D highly links to CVD (AMI, CHF, and stroke) and cancer, as well as other MACCE and the CDC strips.

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Author Contributions

C.H. contributed to conceptualization, methodology, data curation, investigation, visualization, writing-original draft, writing-review & editing; T.T. contributed to conceptualization, data analysis, visualization, writing-review & editing; Q.W. contributed to conceptualization, data analysis, visualization, supervision, writing-review & editing. All the authors read and approved the final manuscript.

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Declaration of Competing Interest

Dr. Tengiz Tkebuchava is affiliated with the company Boston TransTec, LLC, Boston, USA. The other authors have no disclosures to report.

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