Potential Dietary and Lifestyle Interventions for Decreasing Insulin Resistance
Matthew Thomas J. Halma, M.Sc.; Mobeen Syed, M.B.B.S., M.Sc.; Paul E. Marik, M.D.

ABSTRACT

Type 2 diabetes is a growing concern for large segments of the world, and its incidence is rising rapidly, especially in developing nations. Clinical management of type 2 diabetes focuses on managing blood glucose through the provision of oral hypoglycemic drugs, insulin, and more recently GLP-1 agonists and SGLT-2 inhibitors. The expectation is that this is a progressive disease and that patients will remain on these medications lifelong. Given the significant impact on quality of life that diabetes has, it is important to find ways to manage the symptoms and improve insulin sensitivity. Diabetes, along with cardiovascular disease, cancer, and respiratory diseases account for most of non-communicable disease deaths globally. Low-cost and non-invasive treatment of diabetes through diet and supplementation can have significant impacts on global health.

Introduction

Type 2 diabetes mellitus (T2DM) currently affects millions of people globally and is increasing globally, particularly in developing countries.1 Diabetes is creating a massive disease burden and contributing to a lowered quality of life.2 The pathogenesis of diabetes is multifactorial, encompassing genetic and environmental factors, some of which are modifiable.3 Recently, novel treatment approaches demonstrate promise for the long-term remission of T2DM symptoms.4

Diabetes management requires continual use of diabetic medications, with the expectation that this will last life-long. Purchasing the medications, especially the newer call for GLP1-agonists, causes significant economic strain on individuals, insurance companies, and national health services.5

In the U.S., one in every seven health care dollars spent is directly attributable to diabetes, and people with diabetes incur almost one quarter of all medical costs.5 People with diabetes spend $9,601 more per year on medical care than their counterparts without diabetes, and incur $3,640 per year in indirect costs, according to a 2017 survey.5 Adults below the poverty line experience diabetes at higher rates than their more affluent counterparts, and rates of T2DM for adults who do not finish high school (13.4%) are nearly double the rates of those with more than a high school education (7.1%).6 Diabetes rates in different racial populations vary greatly; adults of American Indian origin have the highest rates of diagnosed diabetes at 14.5%, followed by blacks at 12.1%, Hispanics at 11.8%, Asians at 9.5%, and non-Hispanic whites at 7.4%.6

Globally, diabetes affects 6.2% of the world’s population (as of 2017), and one million deaths per year can be attributed to diabetes, making it the ninth leading cause of mortality.7 As nations develop economically, the disease burden of diabetes is increasing fastest in the developing nations of Sub-Saharan Africa, followed by North Africa and the Middle East.1 Eastern Europe saw the slowest rise in T2DM of any geographic region studied.1 Some regions are suffering very high disease prevalence, especially the Pacific Ocean island nations, where prevalence is 20.3% in Fiji, for example.7

T2DM is a challenging issue in developing countries, due to the high relative cost and low accessibility of treatment.6,7 These challenges motivate the search for low-cost and accessible approaches for treatment and prevention of diabetes.

Treatment of diabetes has typically focused on supplying medications over the course of the patient’s life,8 and accepting the permanence of the condition. Early work showed diabetes as a chronic progressive condition, marked by a steady rise in blood glucose4 and degraded pancreatic beta cell function.11 In T2DM, blood sugar increase with disease progression is due to insulin resistance in peripheral tissues, increased glucose production in the liver, and impaired insulin secretion.12 In addition to these three abnormalities, known as the “triumvirate,” five additional pathogenic processes have been added, including accelerated lipolysis in fat cells, incretin hormone deficiency and resistance, overproduction of glucagon, increased renal tubular reabsorption, and long-term potentiation of the central nervous system in metabolic regulation.13 Given the potential complexity of T2DM, the wide variation in individual treatment response must be considered.13 Recent work has demonstrated that long-term remission of T2DM symptoms is possible in a subset of T2DM patients with weight loss,4 and the degree of weight loss is associated with diabetes remission.13

In a subset of T2DM patients undergoing significant weight loss, resumption of ad libitum eating habits did not result in diabetes symptoms returning.13 These findings illustrate the effective treatment of T2DM in a subset of patients, which may guide preventive efforts in the wider population. Treatment based on biological mechanisms could drastically reduce disease burden and medical expenditures on diabetes globally.

Epidemiology

Several factors account for the increased incidence of diabetes. These factors include the increasing consumption of processed food with high glycemic index,14 more sedentary and indoor lifestyles,15 the use of artificial additives, and exposure to pesticides.

Other causes attributable to globalization and modernization may be changed consumption habits associated with increased affluence, and mismatches between one’s ancestral diet and one’s daily diet due to migration or food availability.

A recent survey illustrated the increase in global diabetes between 1990 and projections for 2025. Diabetes prevalence globally has increased from roughly 211 million in 1990 to 476
Changes in Food Consumption Patterns

With increasing affluence and migration to cities, people are more likely to consume processed convenience foods. With convenience foods, people are more likely to eat throughout the day, and processed food provides less sensation of satiety than its natural counterparts, so people can end up consuming more. Additionally, processed food is high in sugar and has a high glycemic index, as blood glucose blunting influences including fiber and protein are separated or removed.

Those purchasing their food from grocery stores are also receiving a less nutritious product than their counterparts even a few decades ago due to mineral depletion of soils and growing technologies, which prioritize bulk mass at the expense of overall health. Artificial sweeteners and other additives can have adverse impacts.

Sedentary, Indoor Lifestyle and Stress

As economic development occurs, people have less need to use their own bodies to perform work. The number of people performing the majority of their work on a computer has risen dramatically, and so have rates of overweight and obesity. Migration to cities and economic affluence are associated with higher rates of sedentary behavior.

In the “Blue Zones,” a term coined by Dan Buettner to describe geographical pockets of people with long health spans, people are active for their entire lifetimes, and low-level physical activity, such as walking or gardening, occurs throughout the day. People exposed to natural settings experience lower levels of stress biomarkers than their counterparts in urban environments. Stress is associated with an impaired glucose response as well as cravings for high glycemic index foods. There are many causes for stress, and loneliness is a major predictor of all-cause mortality and is associated with metabolic health disorders.

Much of modern life takes place indoors, creating fewer opportunities for sun exposure. Sun exposure is inversely correlated with all-cause mortality, and also has positive impacts on metabolism.

Toxic Exposures

Compromise of a regulatory authority has allowed exposure of humans to an increased number of chemicals. Of the chemicals in the U.S. EPA ToxCast screening program, only approximately one-third do not have any toxicity data available, according to a 2009 study. Only one-quarter of chemicals in the ToxCast screening program had an entry in a highly curated database, according to that same study.

Before its 2016 amendment, the U.S. EPA’s Toxic Substances Control Act regulated fewer than 10 chemicals out of a total registered database of more than 86,000 chemicals. Several classes of environmental toxins may play a role in the pathogenesis of diabetes.

Biological Mechanisms: Glucose and Insulin Regulation

Glucose, the body’s primary source of energy, requires insulin, a hormone produced by beta cells in the pancreas, to enter cells for utilization. A common analogy of insulin is as a key to open the cell’s glucose transporter, allowing glucose to enter and power cell functions. This mechanism is essential to maintain proper glucose levels in the bloodstream, and dysregulation of this mechanism leads to hyper- or hypoglycemia.

Insulin resistance is the cornerstone of T2DM, a condition in which peripheral tissues, such as muscle and fat cells, fail to respond effectively to insulin’s signal. Imagine cells as homes with glucose as a guest and insulin as the doorbell. In diabetes, the cells’ metaphorical “occupants” are unresponsive, leading to elevated glucose levels in the blood. High levels of free fatty acids in blood may induce insulin resistance. These fatty acids, often found in excess in obesity, disrupt the internal mechanisms that respond to insulin, preventing the glucose doors from opening. As a result, glucose accumulates in the bloodstream, leading to hyperglycemia and tissue damage.

Beta cells in the pancreas play a critical role in producing insulin. In early stages of T2DM, these cells work overtime to compensate for insulin resistance. However, this overworking comes at a cost. If glucose levels remain elevated due to resistance, beta cells release more insulin, contributing to the glucose influx into cells.

The continual strain causes these cells to produce excess insulin and create additional substances, including amyloid polypeptides. The accumulation of these substances, combined with the inflammatory response triggered by hyperfunction, contributes to beta cell destruction.

The inflammatory response within the pancreas adds another layer to the complexity of diabetes. Macrophages and other immune cells are drawn to the site, leading to a micro-inflammatory environment. These activated immune cells target and destroy beta cells, further exacerbating the condition.

Adipocytes, or fat cells, also have a role to play. In obesity, adipocytes release excessive free fatty acids, which can stimulate the production of inflammatory cytokines, which compunds the inflammatory response, fueling the cycle of insulin resistance and beta cell destruction.

While these obesity-related processes are critically important, the majority of diabetes patients did not reverse their condition after significant weight loss in the DiRECT trial, because of the additional pathogenic processes named above.

Treatment

Diagnostic parameters

Chronically elevated blood glucose is often a sign of insulin resistance (or potentially absolute insulin deficiency, as in the case of type 1 diabetes mellitus), as glucose is inhibited from entering the cell when insulin signaling is not functioning properly. Using the American Diabetes Association diagnostic standards, a fasting plasma glucose (FPG) of 126 mg/dL (7.0mmol/L) or greater is considered diagnostic of diabetes.

Another common test is the hemoglobin A1c test (A1c), which is a proxy measurement for average blood sugar level over the previous 2-3 months. A normal range is between 4% and 5.6%; 5.7% to 6.4% is indicative of prediabetes; and 6.5% and above is diagnostic of diabetes.
Elevated triglycerides (TGs) (>250mg/dL or 2.82mmol/L) can be symptomatic of diabetes. Low high-density lipoprotein (HDL) cholesterol (<35mg/dL or 0.90mmol/L) is also diagnostic of diabetes and pre-diabetes. Importantly for people with diabetes, who are at increased risk of coronary artery disease (CAD), a predictor of CAD is the TG/HDL ratio. Total cholesterol is not predictive of CAD. A ratio of less than 2:1 triglycerides to HDL cholesterol is ideal.

In addition to these possible clarifying tests, suggestive clinical factors include abdominal obesity and hypertension.

**Diet and Lifestyle Changes**

### Meal Timing

- Start with a 1-hour eating window 2 days a week and increase to 6 days a week.
- The ideal is a 1-hour eating window restricted to one meal a day.
- This eating window can be shortened to 4 hours of daily calorie intake.
- Time restricted eating can be accompanied by 30-60 minutes of exercise.

### Meal Composition

- Choose whole, natural, low glycemic index foods.
- Include lots of greens and cruciferous vegetables.
- Avoid processed foods.

### Physical Activity, Sunlight, and Managing Stress

- Avoid excessive endurance exercise, which raises cortisol, blood sugar levels, and weakens insulin responsiveness.
- A 10-mile run, strength training, and walking can be practiced safely by people with diabetes using appropriate hypoglycemic events can increase with fasting.

### Supplements and Medications

- Berberine: lowers blood sugar, improves insulin sensitivity.
- Metformin: improves glycemic control.
- Omega-3: decreases triglycerides.
- Magnesium: reduces blood pressure and improves insulin sensitivity.
- Resveratrol: improves autophagy and longevity.
- cinnamon: reduces blood glucose and insulin resistance.
- Probiotics: improves gut microbial diversity and reduces inflammation, especially in people with diabetes.

**Figure 1.** An Infographics Guide to Interventions Associated with Improvements in T2DM symptoms.

1) Time restricted eating; 2) low glycemic index foods, with emphasis on greens and cruciferous vegetables, while avoiding processed foods; 3) exercise; while avoiding excessive endurance exercise, which can increase cortisol; and sun exposure.

Supplements and medications: a) berberine, b) metformin, c) magnesium, d) melatonin, e) resveratrol, f) cinnamon, g) omega-3, h) probiotics.

Intermittent fasting (IF) can be an effective tool for weight loss and induction of autophagy. As weight loss is associated with a reduction of diabetes in some patients, IF may be an important tool for diabetes management, as it contributes to weight loss, and obese people with diabetes reported spontaneously eating fewer calories. Another benefit of IF for diabetics is alleviation of cognitive impairment, possibly because of changes in gut microbiota.

Using therapeutic fasting, many people have achieved a long-term normalization of their blood sugar and insulin sensitivity parameters without the need for medication. While hypoglycemic events can increase with fasting, fasting can be practiced safely by people with diabetes using appropriate glucose monitoring. However, further research is necessary to elucidate the mechanisms involved in therapeutic fasting in diabetes.

Meals should preferably be composed of foods with a lower glycemic index (GI), which do not raise blood sugar rapidly and can lower fasting blood glucose over the long term. Glycemic index (GI) is a useful metric, which ranks foods from 0 to 100 based on the relative rise in blood glucose level two hours after eating a constant carbohydrate amount (50g) of the measured food. GI varies between individuals, owing to changes in metabolism. The recommendation of the American Diabetes Association low glycemic index diets is equivocal.

Increased consumption of ultra-processed foods (UPFs) is associated with a greater risk of diabetes. Unprocessed fruits and vegetables have low GI despite high carbohydrate levels relative to other macronutrients, possibly owing to their fiber content. Processing can separate the carbohydrates from the fiber matrix and increase the GI. While fruit fiber consumption is weakly protective against diabetes, total fiber consumption shows a lowering of diabetes risk in a dose-responsive manner. Trials on consumption of fruit juices show a neutral or positive correlation between fruit juice consumption and T2DM risk, so unprocessed fruit is a better option.

Despite their lack of calories, artificial sweeteners can increase the risk of diabetes and pose other risks, possibly including cancer. They are proposed to pathogenically alter glucose tolerance through changes in gut microbial composition. However, the herb Stevia rebaudiana, in addition to its use as a sweetener, lowers fasting and post-prandial blood glucose levels in diabetics. Stevia may be an effective natural sweetener for diabetics to use.

A high omega 6:3 ratio, characteristic of modern diets, promotes inflammation. A more balanced ratio of omega-6 to omega-3 (ideally ~1) can reduce inflammation and its contribution to diabetes development. Meta-analyses have shown an improvement in triglycerides, fasting blood glucose, and insulin resistance. However, other meta-analyses of randomized controlled trials (RCTs) did not demonstrate a positive impact of omega-3s on diabetes. Still, dietary changes should prioritize omega-3 consumption over omega-6.

Additionally, even small amounts of trans fatty acids (TFAs) are associated with increased risk of insulin resistance, and should be avoided. TFAs are often found in hydrogenated oils, which are characteristic of UPFs.

Physical activity can be an important intervention in reducing the insulin resistance of people with diabetes.
Medications and Supplements

Several medications and nutritional supplements acting through distinct biological mechanisms are spotlighted here as potentially helpful in diabetes. The American Diabetes Association does not actively recommend any dietary supplements for the treatment of diabetes,87,124 and therefore any dietary supplements are not considered standard of care. Clinical trials are needed to verify benefits and risks.

Berberine is a natural compound known to both traditional Chinese medicine and Ayurvedic medical systems. It is found in many distinct plants and has a history of two millennia of medical use.125 In the context of diabetes, it lowers blood sugar and can reduce insulin resistance.126,127 It is hypothesized to work through mitochondrial inhibition, stimulation of glycolysis, and activation of the AMPK pathway.127

Metformin, one of the best-established anti-diabetic drugs, has actions similar to berberine, lowering blood glucose levels and restoring insulin sensitivity.128

Supplemental magnesium can affect a wide variety of biological pathways, and deficiency is widespread.129 In RCTs, oral magnesium reduces insulin resistance,130 through several mechanisms, which have been covered in a recent review.71

Melatonin, widely known for its role in sleep regulation, has been shown to improve glucose sensitivity in β-cells in an in vitro study.131 Markers associated with insulin resistance increase in cells treated with palmitic acid (common saturated fat), but melatonin inhibits the increased expression of these genes associated with insulin resistance and T2DM.132 Additionally, people who secrete more melatonin during nighttime are less likely to develop insulin resistance.133 These mechanisms are supported by a recent meta-analysis of trials of melatonin on insulin resistance, demonstrating a reduction in diabetes parameters when compared to placebo.134

Resveratrol is useful as a fasting mimetic and can stimulate autophagy.135 In the context of insulin resistance, resveratrol also exhibits autophagy-independent effects.136 A meta-analysis of eleven studies on the impact of resveratrol on insulin resistance demonstrated a significant improvement in insulin sensitivity.73

Cinnamon, in addition to being a common household spice, has also been an herb used in traditional Chinese medicine for at least four millennia.137 A meta-analysis revealed a significant decrease in fasting blood glucose levels,74 marking it as an attractive herb for stabilizing blood sugar levels against rapid fluctuations. Additionally, a meta-analysis of sixteen RCTs demonstrated a significant decrease in the homeostatic model assessment for insulin resistance,138 a metric for insulin resistance.139

Omega-3 fatty acids are important for their cardioprotective effects,140,141 and they also have been observed in a meta-analysis of thirty studies to reduce insulin resistance.118 Since cardiovascular disease is comorbid with diabetes,58 cardioprotective supplements should be considered.

Probiotics can have positive impacts on gut microbial diversity and subsequently have positive impacts on inflammation, inflammatory stress, insulin sensitivity, and reduction in autoimmunity.76,142

Novel pharmaceutical agents

GLP-1 agonists

Glucagon-like peptide-1 (GLP-1) receptor agonists increase glucose-dependent insulin secretion, decrease inappropriate glucagon secretion, delay gastric emptying, and increase satiety.143,144 There are currently six approved GLP-1 receptor agonists: exenatide, lixisenatide, liraglutide, exenatide, dulaglutide and semaglutide. They are administered subcutaneously (SC) at various dosing frequencies, except semaglutide, which is available as a SC and oral formulation. GLP-1 receptor agonists are attractive options for the treatment of T2DM as they effectively lower A1C and weight, while having documented cardiovascular and renal benefits.143,144

A meta-analysis of seven trials, with a combined total of 56,004 participants, demonstrated that treatment with a GLP-1 receptor agonist reduced major cardiovascular events (MACE) by 12% (HR 0.88, 95% CI 0.82-0.94; p<0.0001).145 In this study, the hazard ratios were 0.88 (95% CI 0.81-0.96; p=0.003) for death from cardiovascular causes, 0.84 (0.76-0.93; p<0.0001) for fatal or non-fatal stroke, and 0.91 (0.84-1.00; p=0.043) for fatal or non-fatal myocardial infarction. Furthermore GLP-1 receptor agonist treatment reduced all-cause mortality by 12% (0.88, 0.83-0.95; p=0.001), and also improved composite measures of renal outcome.

The most common adverse effects with the GLP-1 receptor agonists are gastrointestinal related (nausea, vomiting, and diarrhea) and injection site reactions.143 GLP-1 receptor agonists and SGLT-2 inhibitors are strongly recommended by many cardiology and endocrinology societies as first-line therapies ahead of metformin. They also recommend the addition of a GLP-1 agonist in patients who have established atherosclerotic cardiovascular disease,146 heart failure,146 or indicators of established kidney disease.147

The major limitation with the use of GLP-1 agonists is the cost of the drug. In the U.S., a month’s supply costs between $936 and $1,349, although the list price of these drugs is significantly lower in other nations.148 For cost-effectiveness to be achieved, the costs of GLP-1 agonists would have to fall by at least 90%.149

SGLT-2 inhibitors

The SGLT-2 inhibitors comprise a novel class of therapeutics in the treatment of T2DM. It includes canagliflozin, dapagliflozin, ertugliflozin, and empagliflozin.150 The SGLT-2 inhibitors prevent the reabsorption of filtered glucose from the tubular lumen, which lowers blood glucose, as more glucose is excreted in the urine.151,152 In addition to their anti-hyperglycemic effects, they also reduce the risk of major adverse cardiovascular events in patients with T2DM,153 and in patients with pre-existing heart failure.154-156 In addition to cardioprotective effects, they also provide renal protective effects, preventing the decline in glomerular filtration rate (GFR).157 They are attractive drugs for T2DM patients, who are at increased risk of both cardiovascular disease158 and renal failure159 relative to a population without T2DM.

Adverse effects associated with SGLT-2 inhibitors include genital infections, as they increase urine glucose
Dapagliflozin taken at 10 mg daily increased the risk of urinary tract infection compared to placebo (RR 1.33, 1.10–1.61), though this was the only drug-dose combination in the meta-analysis showing a significant result. Even in those with increased genetic susceptibility, significant improvement is possible.

As noted above, the cost of diabetes is a significant fraction of U.S. medical costs. Given that U.S. medical spending constitutes 17.7% of GDP, amounting to $11,172 per person in 2018, the direct costs of diabetes alone are estimated at $1,844 per person per year.

In the U.S., 40% of people would not be able to pay an unexpected expense of $400. In this economic situation, combined with the high cost of insulin, more than one-quarter of U.S. insulin users report rationing insulin in the past year, according to a 2020 survey. As diabetes has a higher prevalence in the lower income deciles, the poor carry a disproportionate share of the burden. The direct cost of diabetes to a patient is $800 per month. For insulin users, costs are rapidly increasing at an annual growth rate of 10%, and the price of insulin tripled between 2002 and 2013. Three companies (Novo Nordisk, Sanofi, and Eli Lilly) control 99% of the world’s market for insulin.

Recent federal legislation limits the maximum price of medications, which include the diabetes medications Jardiance (Boehringer Ingelheim and Eli Lilly), Januvia (Merck), and Farxiga (AstraZeneca), as well as insulin injections produced by Novo Nordisk. This may be of help. But lower-cost treatment would be of enormous benefit.

In contrast to the above, the price of metformin has dropped by 93%. The supplements discussed above plus metformin, cost together around $200 per month.

**Conclusion**

Low-cost solutions are urgently needed for the growing, extremely costly problem of diabetes. There is evidence that the disease burden can be greatly reduced by lifestyle changes, including time-restricted eating of low glycemic-index natural foods, exercise, and sun exposure, with the addition of a few widely available supplements and some medications. The suggested protocols need further study, and funding is needed for holistic diabetes management in medical systems.

Matthew Thomas J. Halma, M.Sc., is affiliated with EbMCsquared, CIC, Bath, UK; Moebeen Syed, M.B.B.S., M.Sc., is founder and CEO of DeBeen Corp.; Paul E. Marik, M.D., is chairman and chief scientific officer, Front Line COVID-19 Critical Care Alliance (FLCCC). Contact: pmarik@flccc.net.

**References**


170. Tanne JH. Biden administration sets out plan to reduce price of 10 drugs used by over 65s that cost $50bn a year. *BMJ* 2023;382:p2022. doi:10.1136/bmj.p2022.