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 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 6.28% 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.[8, p2] 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,[9] and accepting the permanence of the condition. Early work showed diabetes as a chronic progressive condition, marked by a steady rise in blood glucose[10] 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.[12] 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

million in 2017, and is projected to rise to 701million by 2025.[2]

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,[16] and so have rates of overweight and obesity.[17] Migration to cities and economic affluence are associated with higher rates of sedentary behavior.[18,19]

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.[20] People exposed to natural settings experience lower levels of stress biomarkers than their counterparts in urban environments.[21,22] Stress is associated with an impaired glucose response[23] as well as cravings for high glycemic index foods.[24,25] There are many causes for stress, and loneliness is a major predictor of all-cause mortality and is associated with metabolic health disorders.[26]

Much of modern life takes place indoors,[27] creating fewer opportunities for sun exposure. Sun exposure is inversely correlated with all-cause mortality,[28,29] and also has positive impacts on metabolism.[30]

Toxic Exposures

Compromise of a regulatory authority[31] 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.[32] Only one-quarter of chemicals in the ToxCast screening program had an entry in a highly curated database, according to that same study.[32] 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.[33] Several classes of environmental toxins may play a role in the pathogenesis of diabetes.[34–36]

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,[37] 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.[38] This mechanism is essential to maintain proper glucose levels in the bloodstream, and dysregulation of this mechanism leads to hyper- or hypoglycemia.[39]

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.[40] Imagine cells as homes with glucose as a guest and insulin as the doorbell.[41] In diabetes, the cells' metaphorical "occupants" are unresponsive, leading to elevated glucose levels in the blood.[42] 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.[43,44] As a result, glucose accumulates in the bloodstream, leading to hyperglycemia and tissue damage.[45]

Beta cells in the pancreas play a critical role in producing insulin.[37] 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.[46]

The continual strain causes these cells to produce excess insulin and create additional substances, including amyloid polypeptides.[47] The accumulation of these substances,[47] combined with the inflammatory response triggered by hyperfunction,[48] contributes to beta cell destruction.

The inflammatory response within the pancreas adds another layer to the complexity of diabetes.[49,50] Macrophages and other immune cells are drawn to the site, leading to a micro-inflammatory environment.[48] These activated immune cells target and destroy beta cells, further exacerbating the condition.[51,52]

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,[53] which compounds the inflammatory response, fueling the cycle of insulin resistance and beta cell destruction.[48,54]

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,[13] because of the additional pathogenic processes named above.[12]

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.[55] 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.[56]

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.[57] 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.[56]

Elevated triglycerides (TGs) (>250mg/dL or 2.82mmol/L) can be symptomatic of diabetes.[56] Low high-density lipoprotein (HDL) cholesterol (<35mg/dL or 0.90mmol/L) is also diagnostic of diabetes and pre-diabetes.[56] Importantly for people with diabetes, who are at increased risk of coronary artery disease (CAD),[58] a predictor of CAD is the TG/HDL ratio.[59] Total cholesterol is not predictive of CAD.[59] A ratio of less than 2:1 triglycerides to HDL cholesterol is ideal.[60]

In addition to these possible clarifying tests, suggestive clinical factors include abdominal obesity and hypertension.[61]

Diet and Lifestyle Changes

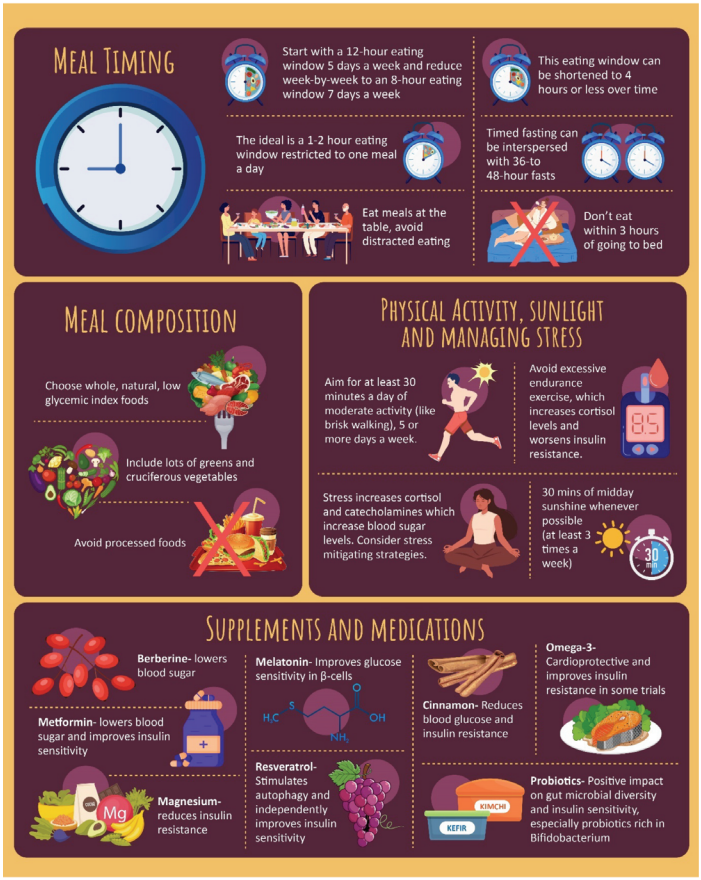

Figure 1. An Infographic Guide to Interventions Associated with Improvements in T2DM symptoms.
1) Time restricted eating;[62] 2) low glycemic index foods,[63] with emphasis on greens and cruciferous vegetables,[64] while avoiding processed foods;[6] 3) exercise,[15] while avoiding excessive endurance exercise, which can increase cortisol,[66] stress reduction,[67] and sun exposure;[68] 4) supplements and medications: a) berberine,[69] b) metformin,[70] c) magnesium,[71] d) melatonin,[72] e) resveratrol,[73] f) cinnamon,[74] g) omega-3,[75] h) probiotics.[76]

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,[13] IF may be an important tool for diabetes management, as it to contributes to weight loss,[77] and obese people with diabetes reported spontaneously eating fewer calories.[78] Another benefit of IF for diabetics is alleviation of cognitive impairment, possibly because of changes in gut microbiota.[79]

Using therapeutic fasting, many people have achieved a long-term normalization of their blood sugar and insulin sensitivity parameters without the need for medication.[80] While hypoglycemic events can increase with fasting,[81] fasting can be practiced safely by people with diabetes using appropriate glucose monitoring.[82] However, further research is necessary to elucidate the mechanisms involved in therapeutic fasting in diabetes.

Meals should preferentially be composed of foods with a lower glycemic index (GI), which do not raise blood sugar rapidly[83] and can lower fasting blood glucose over the long term.[84] 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.[85] GI varies between individuals, owing to changes in metabolism.[86] The recommendation of the American Diabetes Association low glycemic index diets[87] is equivocal.

Increased consumption of ultra-processed foods (UPFs) is associated with a greater risk of diabetes[88–90] and obesity,[91] possibly owing to their higher GI and lower satiety potential.[92] UPFs also contain lower levels of crucial nutrients and fibers[93,94] and higher levels of sugar,[95–97] trans fats,[98] and additives,[99] which contribute to their higher GI relative to less processed food.[92]

Much of the variation in the GI of foods can be attributed to the differential fiber content of the food.[100] Unprocessed fruits and vegetables have low GI despite high carbohydrate levels relative to other macronutrients,[101] possibly owing to their fiber content.[102] Processing can separate the carbohydrates from the fiber matrix and increase the GI.[103] While fruit fiber consumption is weakly protective against diabetes,[104] total fiber consumption shows a lowering of diabetes risk in a dose-responsive manner.[105] Trials on consumption of fruit juices show a neutral[106,107] or positive correlation[108] 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.[109,110] They are proposed to pathogenically alter glucose tolerance through changes in gut microbial composition.[111–113] However, the herb *Stevia rebaudiana*, in addition to its use as a sweetener, lowers fasting and post-prandial blood glucose levels in diabetics.[114] Stevia may be an effective natural sweetener for diabetics to use.

A high omega 6:3 ratio, characteristic of modern diets, promotes inflammation.[115] A more balanced ratio of omega-6 to omega-3 (ideally ~1), can reduce inflammation[115] and its contribution to diabetes development.[116] Meta-analyses have shown an improvement in triglycerides,[117] fasting blood glucose,[118] and insulin resistance.[118] However, other meta-analyses of randomized controlled trials (RCTs) did not demonstrate a positive impact of omega-3s on diabetes.[119,120] 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,[121] and should be avoided. TFAs are often found in hydrogenated oils, which are characteristic of UPFs.[122]

Physical activity can be an important intervention in reducing the insulin resistance of people with diabetes.[66,123]

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 disease[158] and renal failure[159] relative to a population without T2DM.

Adverse effects associated with SGLT-2 inhibitors include genital infections, as they increase urine glucose

concentration.[160,161] 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.[161]

Despite the benefits of SGLT-2 inhibitors and their acceptable safety profile, cost issues are paramount, and the cost of SGLT-2 would need to decrease by 70% to be considered cost effective.[149] The high costs of the GLP-1 agonists and SGLT-2 inhibitors motivate the investigation of lower-cost interventions.

Outlook: Lifting of Disease Burden

Provided that patients are willing to make lifestyle changes, especially in their food consumption patterns, it appears that T2DM is a treatable disorder, as genetic factors only account for 18% of the variability in T2DM risk.[162] 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,[163] 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.[164] 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.[165] As diabetes has a higher prevalence in the lower income deciles,[166] the poor carry a disproportionate share of the burden. The direct cost of diabetes to a patient is $800 per month.[5] For insulin users, costs are rapidly increasing at an annual growth rate of 10%,[167] and the price of insulin tripled between 2002 and 2013.[168] Three companies (Novo Nordisk, Sanofi, and Eli Lilly) control 99% of the world's market for insulin.[169]

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.[170] 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%.[171] 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; **Mobeen Syed, M.B.B.S., M.Sc.,** is founder and CEO of DrBeen 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

1. Liu J, Ren ZH, Qiang H, et al. Trends in the incidence of diabetes mellitus: results from the Global Burden of Disease Study 2017 and implications for diabetes mellitus prevention. *BMC Public Health* 2020;20(1):1415. doi:10.1186/s12889-020-09502-x.
2. Lin X, Xu Y, Pan X, et al. Global, regional, and national burden and trend of diabetes in 195 countries and territories: an analysis from 1990 to 2025. *Sci Rep* 2020;10(1):14790. doi:10.1038/s41598-020-71908-9.
3. Stumvoll M, Goldstein BJ, van Haeften TW. Type 2 diabetes: principles of pathogenesis and therapy. *Lancet* 2005;365(9467):1333-1346. doi:10.1016/S0140-6736(05)61032-X.
4. Lim EL, Hollingsworth KG, Aribisala BS, et al. Reversal of type 2 diabetes: normalisation of beta cell function in association with decreased pancreas and liver triacylglycerol. *Diabetologia* 2011;54(10):2506-2514. doi:10.1007/s00125-011-2204-7.
5. American Diabetes Association. Economic costs of diabetes in the U.S. in 2017. *Diabetes Care* 2018;41(5):917-928. doi:10.2337/dci18-0007.
6. CDC. National Diabetes Statistics Report; Jun 29, 2022. Available at: https://www.cdc.gov/diabetes/data/statistics-report/index.html. Accessed Jun 17, 2023.
7. Khan MAB, Hashim MJ, King JK, et al. Epidemiology of type 2 diabetes—global burden of disease and forecasted trends. *J Epidemiol Glob Health* 2020;10(1):107-111. doi:10.2991/jegh.k.191028.001.
8. Mohan V, Khunti K, Chan SP, et al. Management of type 2 diabetes in developing countries: balancing optimal glycaemic control and outcomes with affordability and accessibility to treatment. *Diabetes Ther* 2020;11(1):15-35. doi:10.1007/s13300-019-00733-9.
9. Bailey C. The current drug treatment landscape for diabetes and perspectives for the future. *Clin Pharmacol Ther* 2015;98(2):170-184. doi:10.1002/cpt.144.
10. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes. *Lancet* 1998;352(9131):837-853. doi:10.1016/S0140-6736(98)07019-6.
11. U.K. Prospective Diabetes Study Group. U.K. prospective diabetes study 16. Overview of 6 years' therapy of type II diabetes: a progressive disease. *Diabetes* 1995;44(11):1249-1258.
12. DeFronzo RA. From the Triumvirate to the Ominous Octet: a new paradigm for the treatment of type 2 diabetes mellitus. *Diabetes* 2009;58(4):773-795. doi:10.2337/db09-9028.
13. Lean ME, Leslie WS, Barnes AC, et al. Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. *Lancet* 2018;391(10120):541-551. doi:10.1016/S0140-6736(17)33102-1.
14. Martins APB, Levy RB, Claro RM, Moubarac JC, Monteiro CA. Increased contribution of ultra-processed food products in the Brazilian diet (1987-2009). *Rev Saúde Pública* 2013;47:656-665. doi:10.1590/S0034-8910.2013047004968.
15. Guthold R, Stevens GA, Riley LM, Bull FC. Worldwide trends in insufficient physical activity from 2001 to 2016: a pooled analysis of 358 population-based surveys with 1.9 million participants. *Lancet Global Health* 2018;6(10):e1077-e1086. doi:10.1016/S2214-109X(18)30357-7.
16. LeBlanc AG, Gunnell KE, Prince SA, et al. The ubiquity of the screen: an overview of the risks and benefits of screen time in our modern world. *Transl J ACSM* 2017;2(17):104. doi:10.1249/TJX.0000000000000039.
17. Maher CA, Mire E, Harrington DM, Staiano AE, Katzmarzyk PT. The independent and combined associations of physical activity and sedentary behavior with obesity in adults: NHANES 2003-06. *Obesity* (Silver Spring) 2013;21(12):E730-737. doi:10.1002/oby.20430.
18. Wang M, Wen X, Zhang Y, Jiang C, Wang F. Is economic environment associated with the physical activity levels and obesity in Chinese adults? A cross-sectional study of 30 regions in China. *BMC Public Health* 2017;17(1):701. doi:10.1186/s12889-017-4699-4.
19. Mielke GI, Brown WJ, Nunes BP, Silva ICM, Hallal PC. Socioeconomic correlates of sedentary behavior in adolescents: systematic review and meta-analysis. *Sports Med* 2017;47(1):61-75. doi:10.1007/s40279-016-0555-4.
20. Buettner D, Skemp S. Blue Zones: lessons from the world's longest lived. *Am J Lifestyle Med* 2016;10(5):318-321. doi:10.1177/1559827616637066.

21. Beil K, Hanes D. The influence of urban natural and built environments on physiological and psychological measures of stress—a pilot study. *Int J Environ Res Public Health* 2013;10(4):1250-1267. doi:10.3390/ijerph10041250.
22. Im SG, Choi H, Jeon YH, et al. Comparison of effect of two-hour exposure to forest and urban environments on cytokine, anti-oxidant, and stress levels in young adults. *Int J Environ Res Public Health* 2016;13(7):625. doi:10.3390/ijerph13070625.
23. Sharma VK, Singh TG. Chronic stress and diabetes mellitus: interwoven pathologies. *Curr Diabetes Rev* 2020;16(6):546-556. doi:10.2174/1573399815666191111152248.
24. Chao A, Grilo CM, White MA, Sinha R. Food cravings mediate the relationship between chronic stress and body mass index. *J Health Pschol* 2015;20(6):721-729. doi:10.1177/1359105315573448.
25. Zellner DA, Saito S, Gonzalez J. The effect of stress on men's food selection. *Appetite* 2007;49(3):696-699. doi:10.1016/j.appet.2007.06.013.
26. Ahmed M, Cerda I, Maloof M. Breaking the vicious cycle: the interplay between loneliness, metabolic illness, and mental health. *Front Psychiatry* 2023;14. Available at: https://www.frontiersin.org/articles/10.3389/fpsyt.2023.1134865. Accessed Jun 20, 2023.
27. Brasche S, Bischof W. Daily time spent indoors in German homes—baseline data for the assessment of indoor exposure of German occupants. *Int Hyg Environ Health* 2005;208(4):247-253. doi:10.1016/j.ijheh.2005.03.003.
28. Lindqvist PG, Epstein E, Nielsen K, et al. Avoidance of sun exposure as a risk factor for major causes of death: a competing risk analysis of the melanoma in Southern Sweden cohort. *J Intern Med* 2016;280(4):375-387. doi:10.1111/joim.12496.
29. Yoon UA, Kim YC, Lee H, et al. The impact of sunlight exposure on mortality of patients with end stage renal disease. *Sci Rep* 2019;9(1):2230. doi:10.1038/s41598-019-38522-w.
30. Tai K, Need AG, Horowitz M, Chapman IM. Vitamin D, glucose, insulin, and insulin sensitivity. *Nutrition* 2008;24(3):279-285. doi:10.1016/j.nut.2007.11.006.
31. Saltelli A, Dankel DJ, Di Fiore M, Holland N, Pigeon M. Science, the endless frontier of regulatory capture. *Futures* 2022;135:102860. doi:10.1016/j.futures.2021.102860.
32. Judson R, Richard A, Dix DJ, et al. The toxicity data landscape for environmental chemicals. *Environ Health Perspect* 2009;117(5):685-695. doi:10.1289/ehp.0800168.
33. Rayasam SDG, Koman PD, Axelrad DA, Woodruff TJ, Chartres N. Toxic Substances Control Act (TSCA) implementation: how the amended law has failed to protect vulnerable populations from toxic chemicals in the United States. *Environ Sci Technol* 2022;56(17):11969-11982. doi:10.1021/acs.est.2c02079.
34. Zeliger HI. Lipophilic chemical exposure as a cause of type 2 diabetes (T2D). *Rev Environ Health* 2013;28(1):9-20. doi:10.1515/reveh-2012-0031.
35. Wei H, Sun J, Shan W, et al. Environmental chemical exposure dynamics and machine learning-based prediction of diabetes mellitus. *Sci Total Environ* 2022;806:150674. doi:10.1016/j.scitotenv.2021.150674.
36. Leso V, Capitanelli I, Lops EA, Ricciardi W, Iavicoli I. Occupational chemical exposure and diabetes mellitus risk. *Toxicol Ind Health* 2017;33(3):222-249. doi:10.1177/0748233715624594.
37. Boland BB, Rhodes CJ, Grimsby JS. The dynamic plasticity of insulin production in β-cells. *Molec Metab* 2017;6(9):958-973. doi:10.1016/j.molmet.2017.04.010.
38. Czech MP, Corvera S. Signaling mechanisms that regulate glucose transport. *J Biol Chem* 1999;274(4):1865-1868. doi:10.1074/jbc.274.4.1865.
39. Khan A, Pessin J. Insulin regulation of glucose uptake: a complex interplay of intracellular signalling pathways. *Diabetologia* 2002;45(11):1475-1483. doi:10.1007/s00125-002-0974-7.
40. Shulman GI. Cellular mechanisms of insulin resistance. *J Clin Invest* 2000;106(2):171-176. doi:10.1172/JCI10583.
41. Lizcano JM, Alessi DR. The insulin signalling pathway. *Curr Biol* 2002;12(7):R236-R238. doi:10.1016/S0960-9822(02)00777-7.
42. Reaven GM, Olefsky JM. The role of insulin resistance in the pathogenesis of diabetes mellitus. In: Miller M, Bennett PH, eds. *Advances in Metabolic Disorders*. Vol 9. Elsevier; 1978:313-331. doi:10.1016/B978-0-12-027309-6.50021-5.
43. Boden G. Obesity, insulin resistance and free fatty acids. *Curr Opin Endocrinol Diabetes Obes.* 2011;18(2):139-143. doi:10.1097/MED.0b013e3283444b09.
44. Boden G. Free fatty acids, insulin resistance, and type 2 diabetes mellitus. *Proc Assoc Am Physicians* 1999;111(3):241-248. doi:10.1046/j.1525-1381.1999.99220.x.
45. Robertson RP, Harmon JS. Diabetes, glucose toxicity, and oxidative stress: a case of double jeopardy for the pancreatic islet β cell. *Free Radic Biol Med* 2006;41(2):177-184. doi:10.1016/j.freeradbiomed.2005.04.030.
46. Weir GC, Bonner-Weir S. Five stages of evolving beta-cell dysfunction during progression to diabetes. *Diabetes* 2004;53(suppl_3):S16-S21. doi:10.2337/diabetes.53.suppl_3.S16.
47. Marzban L, Park K, Verchere CB. Islet amyloid polypeptide and type 2 diabetes. *Exp Gerontol* 2003;38(4):347-351. doi:10.1016/S0531-5565(03)00004-4.
48. Devaraj S, Dasu MR, Jialal I. Diabetes is a proinflammatory state: a translational perspective. *Expert Rev Endocrinol Metab* 2010;5(1):19-28. doi:10.1586/eem.09.44.
49. Igoillo-Esteve M, Marselli L, Cunha DA, et al. Palmitate induces a pro-inflammatory response in human pancreatic islets that mimics CCL2 expression by beta cells in type 2 diabetes. *Diabetologia* 2010;53(7):1395-1405. doi:10.1007/s00125-010-1707-y.
50. Akash MSH, Rehman K, Chen S. Role of inflammatory mechanisms in pathogenesis of type 2 diabetes mellitus. *J Cellular Biochem* 2013;114(3):525-531. doi:10.1002/jcb.24402.
51. Rabinovitch A, Suarez-Pinzon WL. Cytokines and their roles in pancreatic islet β-cell destruction and insulin-dependent diabetes mellitus. *Biochem Pharmacol* 1998;55(8):1139-1149. doi:10.1016/S0006-2952(97)00492-9.
52. Thomas HE, McKenzie MD, Angstetra E, Campbell PD, Kay TW. Beta cell apoptosis in diabetes. *Apoptosis* 2009;14(12):1389-1404. doi:10.1007/s10495-009-0339-5.
53. Keller U. From obesity to diabetes. *Int J Vitam Nutr Res* 2006;76(4):172-177. doi:10.1024/0300-9831.76.4.172.
54. McDaniel ML, Kwon G, Hill JR, Marshall CA, Corbett JA. Cytokines and nitric oxide in islet inflammation and diabetes. *Proc Soc Exp Biol Med* 1996;211(1):24-32. doi:10.3181/00379727-211-43950D.
55. James DE, Stöckli J, Birnbaum MJ. The aetiology and molecular landscape of insulin resistance. *Nat Rev Mol Cell Biol* 2021;22(11):751-771. doi:10.1038/s41580-021-00390-6.
56. American Diabetes Association. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes—2021. *Diabetes Care* 2021;44(Suppl 1):S15-S33. doi:10.2337/dc21-S002.
57. Gallagher EJ, Le Roith D, Bloomgarden Z. Review of hemoglobin A1c in the management of diabetes. *J Diabetes* 2009;1(1):9-17. doi: 10.1111/j.1753-0407.2009.00009.x.
58. Glovaci D, Fan W, Wong ND. Epidemiology of diabetes mellitus and cardiovascular disease. *Curr Cardiol Rep* 2019;21(4):21. doi:10.1007/s11886-019-1107-y.
59. Da Luz PL, Favarato D, Faria-Neto Jr JR, Lemos P, Chagas ACP. High ratio of triglycerides to HDL-cholesterol predicts extensive coronary disease. *Clinics* 2008;63:427-432. doi:10.1590/S1807-59322008000400003.
60. Xia W, Yao X, Chen Y, et al. Elevated TG/HDL-C and non-HDL-C/HDL-C ratios predict mortality in peritoneal dialysis patients. *BMC Nephrol* 2020;21(1):324. doi:10.1186/s12882-020-01993-5.
61. Huang PL. A comprehensive definition for metabolic syndrome. *Dis Model Mech* 2009;2(5-6):231-237. doi:10.1242/dmm.001180.
62. Fanti M, Mishra A, Longo VD, Brandhorst S. Time-restricted eating, intermittent fasting, and fasting-mimicking diets in weight loss. *Curr Obes Rep* 2021;10(2):70-80. doi:10.1007/s13679-021-00424-2.
63. Yari Z, Behrouz V, Zand H, Pourvali K. New insight into diabetes management: from glycemic index to dietary insulin index. *Curr Diabetes Rev* 2020;16(4):293-300. doi:10.2174/1573399815666190614122626.
64. Pokharel P, Kyrø C, Olsen A, et al. Vegetable, but not potato, intake is associated with a lower risk of type 2 diabetes in the Danish diet, cancer and health cohort. *Diabetes Care* 2023;46(2):286-296. doi:10.2337/dc22-0974.
65. Schwingshackl L, Hoffmann G, Lampousi AM, et al. Food groups and risk of type 2 diabetes mellitus: a systematic review and meta-analysis of prospective studies. *Eur J Epidemiol* 2017;32(5):363-375. doi:10.1007/s10654-017-0246-y.
66. Magkos F, Hjorth MF, Astrup A. Diet and exercise in the prevention and treatment of type 2 diabetes mellitus. *Nat Rev Endocrinol* 2020;16(10):545-555. doi:10.1038/s41574-020-0381-5.

67. Hackett RA, Steptoe A. Type 2 diabetes mellitus and psychological stress—a modifiable risk factor. *Nat Rev Endocrinol* 2017;13(9):547-560. doi:10.1038/nrendo.2017.64.
68. Shore-Lorenti C, Brennan SL, Sanders KM, et al. Shining the light on sunshine: a systematic review of the influence of sun exposure on type 2 diabetes mellitus-related outcomes. *Clin Endocrinol* (Oxford) 2014;81(6):799-811. doi:10.1111/cen.12567.
69. Yin J, Xing H, Ye J. Efficacy of berberine in patients with type 2 diabetes mellitus. *Metabolism* 2008;57(5):712-717. doi:10.1016/j.metabol.2008.01.013.
70. Pernicova I, Korbonits M. Metformin—mode of action and clinical implications for diabetes and cancer. *Nat Rev Endocrinol* 2014;10(3):143-156. doi:10.1038/nrendo.2013.256.
71. Kostov K. effects of magnesium deficiency on mechanisms of insulin resistance in type 2 diabetes: focusing on the processes of insulin secretion and signaling. *Int J Mol Sci* 2019;20(6):1351. doi:10.3390/ijms20061351.
72. Delpino FM, Figueiredo LM, Nunes BP. Effects of melatonin supplementation on diabetes: a systematic review and meta-analysis of randomized clinical trials. *Clin Nutr* 2021;40(7):4595-4605. doi:10.1016/j.clnu.2021.06.007.
73. Liu K, Zhou R, Wang B, Mi MT. Effect of resveratrol on glucose control and insulin sensitivity: a meta-analysis of 11 randomized controlled trials. *Am J Clin Nutr* 2014;99(6):1510-1519. doi:10.3945/ajcn.113.082024.
74. Allen RW, Schwartzman E, Baker WL, Coleman CI, Phung OJ. Cinnamon use in type 2 diabetes: an updated systematic review and meta-analysis. *Ann Fam Med* 2013;11(5):452-459. doi:10.1370/afm.1517.
75. Delpino FM, Figueiredo LM, Da Silva BGC, et al. Omega-3 supplementation and diabetes: a systematic review and meta-analysis. *Crit Rev Food Sci Nutr* 2022;62(16):4435-4448. doi:10.1080/10408398.2021.1875977.
76. Tao YW, Gu YL, Mao XQ, Zhang L, Pei YF. Effects of probiotics on type II diabetes mellitus: a meta-analysis. *J Transl Med* 2020;18(1):30. doi:10.1186/s12967-020-02213-2.
77. Borgundvaag E, Mak J, Kramer CK. Metabolic impact of intermittent fasting in patients with type 2 diabetes mellitus: a systematic review and meta-analysis of interventional studies. *J Clin Endocrinol Metab* 2021;106(3):902-911. doi:10.1210/clinem/dgaa926.
78. Arnason TG, Bowen MW, Mansell KD. Effects of intermittent fasting on health markers in those with type 2 diabetes: a pilot study. *World J Diabetes* 2017;8(4):154-164. doi:10.4239/wjd.v8.i4.154.
79. Liu Z, Dai X, Zhang H, et al. Gut microbiota mediates intermittent-fasting alleviation of diabetes-induced cognitive impairment. *Nat Commun* 2020;11(1):855. doi:10.1038/s41467-020-14676-4.
80. Furmli S, Elmasry R, Ramos M, Fung J. Therapeutic use of intermittent fasting for people with type 2 diabetes as an alternative to insulin. *Case Reports* 2018;2018:bcr. doi:10.1136/bcr-2017-221854.
81. Corley BT, Carroll RW, Hall RM, et al. Intermittent fasting in type 2 diabetes mellitus and the risk of hypoglycaemia: a randomized controlled trial. *Diabetic Med* 2018;35(5):588-594. doi:10.1111/dme.13595.
82. Grajower MM, Horne BD. Clinical management of intermittent fasting in patients with diabetes mellitus. *Nutrients* 2019;11(4):873. doi:10.3390/nu11040873.
83. Vlachos D, Malisova S, Lindberg FA, Karaniki G. Glycemic index (GI) or glycemic load (GL) and dietary interventions for optimizing postprandial hyperglycemia in patients with T2 diabetes: a review. *Nutrients* 2020;12(6):1561. doi:10.3390/nu12061561.
84. Zafar MI, Mills KE, Zheng J, et al. Low-glycemic index diets as an intervention for diabetes: a systematic review and meta-analysis. *Am J Clin Nutr* 2019;110(4):891-902. doi:10.1093/ajcn/nqz149.
85. Arvidsson-Lenner R, Asp NG, Axelsen M, et al. Glycaemic Index. *Scand J Nutr* 2004;48(2):84-94. doi:10.1080/11026480410033999.
86. Matthan NR, Ausman LM, Meng H, Tighiouart H, Lichtenstein AH. Estimating the reliability of glycemic index values and potential sources of methodological and biological variability. *Am J Clin Nutr* 2016;104(4):1004-1013. doi:10.3945/ajcn.116.137208.
87. El Sayed NA, Aleppo G, Aroda VR, et al. 5. Facilitating positive health behaviors and well-being to improve health outcomes: standards of care in diabetes—2023. *Diabetes Care* 2022;46(Supplement_1):S68-S96. doi:10.2337/dc23-S005.
88. Levy RB, Rauber F, Chang K, et al. Ultra-processed food consumption and type 2 diabetes incidence: A prospective cohort study. *Clin Nutr* 2021;40(5):3608-3614. doi:10.1016/j.clnu.2020.12.018.
89. Moradi S, Kermani MAH, Bagheri R, et al. Ultra-processed food consumption and adult diabetes risk: a systematic review and dose-response meta-analysis. *Nutrients* 2021;13(12):4410. doi:10.3390/nu13124410.
90. Delpino FM, Figueiredo LM, Bielemann RM, et al. Ultra-processed food and risk of type 2 diabetes: a systematic review and meta-analysis of longitudinal studies. *Int J Epidemiol* 2022;51(4):1120-1141. doi:10.1093/ije/dyab247.
91. Nardocci M, Polsky JY, Moubarac JC. Consumption of ultra-processed foods is associated with obesity, diabetes and hypertension in Canadian adults. *Can J Public Health* 2021;112(3):421-429. doi:10.17269/s41997-020-00429-9.
92. Fardet A. Minimally processed foods are more satiating and less hyperglycemic than ultra-processed foods: a preliminary study with 98 ready-to-eat foods. *Food & Function* 2016;7(5):2338-2346. doi:10.1039/C6FO00107F.
93. Da Costa Louzada ML, Martins APB, Canella DS, et al. Impact of ultra-processed foods on micronutrient content in the Brazilian diet. *Rev Saude Publica* 2015;49:45. doi:10.1590/S0034-8910.2015049006211.
94. Moubarac JC, Batal M, Louzada ML, Martinez Steele E, Monteiro CA. Consumption of ultra-processed foods predicts diet quality in Canada. *Appetite* 2017;108:512-520. doi:10.1016/j.appet.2016.11.006.
95. Poti JM, Mendez MA, Ng SW, Popkin BM. Is the degree of food processing and convenience linked with the nutritional quality of foods purchased by US households? *Am J Clin Nutr* 2015;101(6):1251-1262. doi:10.3945/ajcn.114.100925.
96. Cediel G, Reyes M, Louzada ML, et al. Ultra-processed foods and added sugars in the Chilean diet (2010). *Pub Health Nutr* 2018;21(1):125-133. doi:10.1017/S1368980017001161.
97. Steele ME, Baraldi LG, Louzada ML, et al. Ultra-processed foods and added sugars in the US diet: evidence from a nationally representative cross-sectional study. *BMJ Open* 2016;6(3):e009892. doi:10.1136/bmjopen-2015-009892.
98. Silveira BM, Gonzalez-Chica DA, da Costa Proença RP. Reporting of trans-fat on labels of Brazilian food products. *Pub Health Nutr* 2013;16(12):2146-2153.
99. Chassaing B, Koren O, Goodrich JK, et al. Dietary emulsifiers impact the mouse gut microbiota promoting colitis and metabolic syndrome. *Nature* 2015;519(7541):92-96. doi:10.1038/nature14232.
100. Wolever T. Relationship between dietary fiber content and composition in foods and the glycemic index. *Am J Clin Nutr* 1990;51(1):72-75. doi:10.1093/ajcn/51.1.72.
101. Passos TU, de Carvalho Sampaio HA, Sabry MOD, et al. Glycemic index and glycemic load of tropical fruits and the potential risk for chronic diseases. *Food Sci Technol* 2015;35:66-73. doi:10.1590/1678-457X.6449.
102. Slavin JL, Lloyd B. Health benefits of fruits and vegetables. *Adv Nutr* 2012;3(4):506-516. doi:10.3945/an.112.002154.
103. Crummett LT, Grosso RJ. Postprandial glycemic response to whole fruit versus blended fruit in healthy, young adults. *Nutrients* 2022;14(21):4565. doi:10.3390/nu14214565.
104. The InterAct Consortium. Dietary fibre and incidence of type 2 diabetes in eight European countries: the EPIC-InterAct Study and a meta-analysis of prospective studies. *Diabetologia* 2015;58(7):1394-1408. doi:10.1007/s00125-015-3585-3589.
105. Yao B, Fang H, Xu W, et al. Dietary fiber intake and risk of type 2 diabetes: a dose–response analysis of prospective studies. *Eur J Epidemiol* 2014;29(2):79-88. doi:10.1007/s10654-013-9876-x.
106. Eshak ES, Iso H, Mizoue T, et al. Soft drink, 100% fruit juice, and vegetable juice intakes and risk of diabetes mellitus. *Clin Nutr* 2013;32(2):300-308. doi:10.1016/j.clnu.2012.08.003.
107. Xi B, Li S, Liu Z, et al. Intake of fruit juice and incidence of type 2 diabetes: a systematic review and meta-analysis. *PLOS ONE* 2014;9(3):e93471. doi:10.1371/journal.pone.0093471.
108. Bazzano LA, Li TY, Joshipura KJ, Hu FB. Intake of fruit, vegetables, and fruit juices and risk of diabetes in women. *Diabetes Care* 2008;31(7):1311-1317. doi:10.2337/dc08-0080.
109. Purohit V, Mishra S. The truth about artificial sweeteners—are they good for diabetics? *Indian Heart J* 2018;70(1):197-199. doi:10.1016/j.ihj.2018.01.020.

110. Iizuka K. Is the use of artificial sweeteners beneficial for patients with diabetes mellitus? The advantages and disadvantages of artificial sweeteners. *Nutrients* 2022;14(21):4446. doi:10.3390/nu14214446.
111. Page KA. A gut reaction: microbiome-driven glycemic effects of non-nutritive sweeteners. *Cell* 2022;185(18):3282-3284.
112. Ruiz-Ojeda FJ, Plaza-Díaz J, Sáez-Lara MJ, Gil A. Effects of sweeteners on the gut microbiota: a review of experimental studies and clinical trials. *Adv Nutr* 2019;10:S31-S48. doi:10.1093/advances/nmy037.
113. Suez J, Cohen Y, Valdés-Mas R, et al. Personalized microbiome-driven effects of non-nutritive sweeteners on human glucose tolerance. *Cell* 2022;185(18):3307-3328.
114. Ritu M, Nandini J. Nutritional composition of Stevia rebaudiana, a sweet herb, and its hypoglycaemic and hypolipidaemic effect on patients with non-insulin dependent diabetes mellitus. *J Sci Food Agric* 2016;96(12):4231-4234. doi:10.1002/jsfa.7627.
115. Simopoulos AP. Omega-6/omega-3 essential fatty acid ratio and chronic diseases. *Food Rev Int* 2004;20(1):77-90. doi:10.1081/FRI-120028831.
116. Chait A, den Hartigh LJ. Adipose tissue distribution, inflammation and its metabolic consequences, including diabetes and cardiovascular disease. *Front Cardiovasc Med* 2020;7. Available at: https://www.frontiersin.org/articles/10.3389/fcvm.2020.00022. Accessed Jun 12, 2023.
117. Hartweg J, Perera R, Montori VM, et al. Omega-3 polyunsaturated fatty acids (PUFA) for type 2 diabetes mellitus. *Cochrane Database Syst Rev* 2008;(1). doi:10.1002/14651858.CD003205.pub2.
118. Delpino FM, Figueiredo LM, da Silva BGC, et al. Omega-3 supplementation and diabetes: a systematic review and meta-analysis. *Crit Rev Food Sci Nutr* 2022;62(16):4435-4448. doi:10.1080/10408398.2021.1875977.
119. Brown TJ, Brainard J, Song F, et al. Omega-3, omega-6, and total dietary polyunsaturated fat for prevention and treatment of type 2 diabetes mellitus: systematic review and meta-analysis of randomised controlled trials. *BMJ* 2019;366:l4697. doi:10.1136/bmj.l4697.
120. Wu JHY, Micha R, Imamura F, et al. Omega-3 fatty acids and incident type 2 diabetes: a systematic review and meta-analysis. *Brit J Nutr* 2012;107(S2):S214-S227. doi:10.1017/S0007114512001602.
121. Micha R, Mozaffarian D. Trans fatty acids: effects on metabolic syndrome, heart disease and diabetes. *Nat Rev Endocrinol* 2009;5(6):335-344. doi:10.1038/nrendo.2009.79.
122. Ogari AF. Source, extraction and constituents of fats and oils. *J Food Sci Nutr*, Apr 20, 2020. doi:10.24966/FSN-1076/100060.
123. Sampath Kumar A, Maiya AG, Shastry BA, et al. Exercise and insulin resistance in type 2 diabetes mellitus: a systematic review and meta-analysis. *Ann Phys Rehab Med* 2019;62(2):98-103. doi:10.1016/j.rehab.2018.11.001.
124. American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes—2021. *Diabetes Care* 2020;44(Supplement_1):S111-S124. doi:10.2337/dc21-S009.
125. Birdsall T. Berberine: therapeutic potential of alkaloid found in several medicinal plants. *Altern Med Rev* 1997;2:94-103.
126. Yin J, Xing H, Ye J. Efficacy of berberine in patients with type 2 diabetes mellitus. *Metabolism* 2008;57(5):712-717. doi:10.1016/j.metabol.2008.01.013.
127. Yin J, Ye J, Jia W. Effects and mechanisms of berberine in diabetes treatment. *Acta Pharmaceutica Sinica B* 2012;2(4):327-334. doi:10.1016/j.apsb.2012.06.003.
128. Pernicova I, Korbonits M. Metformin—mode of action and clinical implications for diabetes and cancer. *Nat Rev Endocrinol* 2014;10(3):143-156. doi:10.1038/nrendo.2013.256.
129. Johnson S. The multifaceted and widespread pathology of magnesium deficiency. *Med Hypotheses* 2001;56(2):163-170. doi:10.1054/mehy.2000.1133.
130. Mooren FC, Krüger K, Völker K, et al. Oral magnesium supplementation reduces insulin resistance in non-diabetic subjects—a double-blind, placebo-controlled, randomized trial. *Diabetes Obes Metab* 2011;13(3):281-284. doi:10.1111/j.1463-1326.2010.01332.x.
131. Ramracheya RD, Muller DS, Squires PE, et al. Function and expression of melatonin receptors on human pancreatic islets. *J Pineal Res* 2008;44(3):273-279. doi:10.1111/j.1600-079X.2007.00523.x.
132. Heo JI, Yoon DW, Yu JH, et al. Melatonin improves insulin resistance and hepatic steatosis through attenuation of alpha-2-HS-glycoprotein. *J Pineal Res* 2018;65(2). doi:10.1111/jpi.12493.
133. McMullan CJ, Curhan GC, Schernhammer ES, Forman JP. Association of nocturnal melatonin secretion with insulin resistance in nondiabetic young women. *Am J Epidemiol* 2013;178(2):231-238. doi:10.1093/aje/kws470.
134. Delpino FM, Figueiredo LM, Nunes BP. Effects of melatonin supplementation on diabetes: a systematic review and meta-analysis of randomized clinical trials. *Clin Nutr* 2021;40(7):4595-4605. doi:10.1016/j.clnu.2021.06.007.
135. Chatam O, Chapnik N, Froy O. Resveratrol induces the fasting state and alters circadian metabolism in hepatocytes. *Plant Foods Hum Nutr* 2022;77(1):128-134. doi:10.1007/s11130-022-00954-7.
136. Barber TM, Kabisch S, Randeva HS, Pfeiffer AFH, Weickert MO. Implications of resveratrol in obesity and insulin resistance: a state-of-the-art review. *Nutrients* 2022;14(14):2870. doi:10.3390/nu14142870.
137. Shen Y, Jia LN, Honma N, et al. Beneficial effects of cinnamon on the metabolic syndrome, inflammation, and pain, and mechanisms underlying these effects—a review. *J Tradit Complement Med* 2012;2(1):27-32. doi:10.1016/s2225-4110(16)30067-0.
138. Deyno S, Eneyew K, Seyfe S, et al. Efficacy and safety of cinnamon in type 2 diabetes mellitus and pre-diabetes patients: a meta-analysis and meta-regression. *Diabetes Res Clin Pract* 2019;156:107815. doi:10.1016/j.diabres.2019.107815.
139. Matthews DR, Hosker JP, Rudenski AS, et al. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985;28(7):412-419. doi:10.1007/BF00280883.
140. Zelniker TA, Morrow DA, Scirica BM, et al. Plasma omega-3 fatty acids and the risk of cardiovascular events in patients after an acute coronary syndrome in MERLIN-TIMI 36. *J Am Heart Assoc* 2021;10(8):e017401. doi:10.1161/JAHA.120.017401.
141. Toko H, Morita H, Katakura M, et al. Omega-3 fatty acid prevents the development of heart failure by changing fatty acid composition in the heart. *Sci Rep* 2020;10(1):15553. doi:10.1038/s41598-020-72686-0.
142. Gomes AC, Bueno AA, de Souza RGM, Mota JF. Gut microbiota, probiotics and diabetes. *Nutr J* 2014;13(1):60. doi:10.1186/1475-2891-13-60.
143. Trujillo JM, Nuffer W, Smith BA. GLP-1 receptor agonists: an updated review of head-to-head clinical studies. *Ther Adv Endocrinol Metab* 2021;12(Mar 9):2042018821997320. doi:10.1177/2042018821997320.
144. Pandey S, Mangmool S, Parichatikanond W. Multifaceted roles of GLP-1 and its analogs: a review on molecular mechanisms with a cardiotherapeutic perspective. *Pharmaceuticals* 2023;16(6):836. doi:10.3390/ph16060836.
145. Kristensen SL, Rørth R, Jhund PS, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet Diabetes Endocrinol* 2019;7(10):776-785. doi:10.1016/S2213-8587(19)30249-9146.
147. Chen JJ, Wu CY, Jenq CC, et al. Association of glucagon-like peptide-1 receptor agonist vs dipeptidyl peptidase-4 inhibitor use with mortality among patients with type 2 diabetes and advanced chronic kidney disease. *JAMA Network Open* 2022;5(3):e221169. doi:10.1001/jamanetworkopen.2022.1169.
148. Amin K, Telesford I, Singh R, Cox C. How do prices of drugs for weight loss in the U.S. compare to peer nations' prices? Peterson-KFF Health System Tracker. Available at: https://www.healthsystemtracker.org/brief/prices-of-drugs-for-weight-loss-in-the-us-and-peer-nations/. Accessed Oct 21, 2023.
149. Choi JG, Winn AN, Skandari MR, et al. First-line therapy for type 2 diabetes with sodium–glucose cotransporter-2 inhibitors and glucagon-like peptide-1 receptor agonists. *Ann Intern Med* 2022;175(10):1392-1400. doi:10.7326/M21-2941.
150. Nespoux J, Vallon V. Renal effects of SGLT2 inhibitors: an update. *Curr Opin Nephrol Hypertens* 2020;29(2):190-198. doi:10.1097/MNH.0000000000000584.
151. Vallon V, Thomson SC. Targeting renal glucose reabsorption to treat hyperglycaemia: the pleiotropic effects of SGLT2 inhibition. *Diabetologia* 2017;60(2):215-225. doi:10.1007/s00125-016-4157-3.

152. Abdul-Ghani MA, Norton L, DeFronzo RA. Renal sodium-glucose cotransporter inhibition in the management of type 2 diabetes mellitus. *Am J Physiol Renal Physiol* 2015;309(11):F889-F900. doi:10.1152/ajprenal.00267.2015.
153. Zelniker TA, Wiviott SD, Raz I, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet* 2019;393(10166):31-39. doi:10.1016/S0140-6736(18)32590-X.
154. Monzo L, Ferrari I, Cicogna F, Tota C, Calò L. Sodium-glucose co-transporter-2 inhibitors eligibility in patients with heart failure with reduced ejection fraction. *Int J Cardiol* 2021;341:56-59. doi:10.1016/j.ijcard.2021.08.035.
155. Pabel S, Hamdani N, Singh J, Sossalla S. Potential mechanisms of SGLT2 inhibitors for the treatment of heart failure with preserved ejection fraction. *Front Physiol* 2021;12:752370. doi:10.3389/fphys.2021.752370.
156. Solomon SD, McMurray JJV, Claggett B, et al. Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. *N Engl J Med* 2022;387(12):1089-1098. doi:10.1056/NEJMoa2206286.
157. Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med* 2020;383(15):1436-1446. doi:10.1056/NEJMoa2024816.
158. Martín-Timón I, Sevillano-Collantes C, Segura-Galindo A, del Cañizo-Gómez FJ. Type 2 diabetes and cardiovascular disease: have all risk factors the same strength? *World J Diabetes* 2014;5(4):444-470. doi:10.4239/wjd.v5.i4.444.
159. Nasri H, Rafieian-Kopaei M. Diabetes mellitus and renal failure: prevention and management. *J Res Med Sci* 2015;20(11):1112-1120. doi:10.4103/1735-1995.172845.
160. Halimi S, Vergès B. Adverse effects and safety of SGLT-2 inhibitors. *Diabetes Metab* 2014;40(6, Supplement 1):S28-S34. doi:10.1016/S1262-3636(14)72693-X.
161. Puckrin R, Saltiel MP, Reynier P, et al. SGLT-2 inhibitors and the risk of infections: a systematic review and meta-analysis of randomized controlled trials. *Acta Diabetol* 2018;55(5):503-514. doi:10.1007/s00592-018-1116-0.
162. Mahajan A, Taliun D, Thurner M, et al. Fine-mapping type 2 diabetes loci to single-variant resolution using high-density imputation and islet-specific epigenome maps. *Nat Genet* 2018;50(11):1505-1513. doi:10.1038/s41588-018-0241-6.
163. Hartman M, Martin AB, Benson J, Catlin A, National Health Expenditures Account Team. National health care spending in 2018: growth driven by accelerations in Medicare and private insurance spending. *Health Affairs* 2020;39(1):8-17. doi:10.1377/hlthaff.2019.01451.
164. Chen L, Duchan C, Durante A, et al. Consumer and Community Research Section of the Federal Reserve Board's Division of Consumer and Community Affairs (DCCA). Report on the Economic Well-Being of U.S. Households in 2018. Board of Governors of the Federal Reserve System; May 2019:1-64. Available at: https://www.federalreserve.gov/publications/files/2018-report-economic-well-being-us-households-201905.pdf. Accessed Nov 21, 2023.
165. Pfiester E, Braune K, Thieffry A, et al. Costs and underuse of insulin and diabetes supplies: findings from the 2020 T1International cross-sectional web-based survey. *Diabetes Res Clin Pract* 2021;179:108996. doi:10.1016/j.diabres.2021.108996.
166. Hill-Briggs F, Adler NE, Berkowitz SA, et al. Social determinants of health and diabetes: a scientific review. *Diabetes Care* 2020;44(1):258-279. doi:10.2337/dci20-0053.
167. Cefalu WT, Dawes DE, Gavlak G, et al. Insulin Access and Affordability Working Group: Conclusions and recommendations. *Diabetes Care* 2018;41(6):1299-1311. doi:10.2337/dci18-0019.
168. Hua X, Carvalho N, Tew M, et al. Expenditures and prices of antihyperglycemic medications in the United States: 2002-2013. *JAMA* 2016;315(13):1400-1402. doi:10.1001/jama.2016.0126.
169. Beran D, Ewen M, Laing R. Constraints and challenges in access to insulin: a global perspective. *Lancet Diabetes Endocrinol* 2016;4(3):275-285. doi:10.1016/S2213-8587(15)00521-5.
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.