

## MANAGING THE DIABETES EPIDEMIC

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As global populations gain affluence, the incidence rates of diabetes have soared. The disease is segmented into two types. Type 1 diabetes mellitus is an organ-specific autoimmune disease that destroys insulin-secreting beta cells by immune-mediated inflammation. Type 2 diabetes mellitus is a metabolic disease. Both are characterized by insufficient insulin production.

People with type 2 diabetes are at high risk of developing a plethora of additional diseases, including cardiovascular disease, renal disease, peripheral vascular disease, nerve disease, neuropathic pain, erectile dysfunction, skin ulceration, cataracts and cirrhosis, as well as increased risks from falls, bone fractures and cognitive decline.<sup>i</sup> Currently, more than 170 million people throughout the world have developed diabetes (type 1 and 2 combined), and that number is expected to more than double by 2030.<sup>ii</sup> In the U.S., the cost of treatment was estimated at \$174 billion in 2007. As the

burden grows, existing models of the disease and management assumptions are being challenged.

New scientific studies are finding links beyond the well-established models of diet and exercise to include studies of human nutrition, the gut microbiome, the internal and external chemical environment and genetic factors. This expanding understanding of the onset and progression of diabetes is leading to an entirely new diagnostic development opportunity to detect diabetes, identify new surrogate endpoints, delineate possible stages of disease progression, predict age of onset, guide a dietary regime, and to potentially drive new tailored treatment protocols. Although exercise and dietary modification remain key elements in preventing or delaying onset and severity, emerging approaches may include administering new classes of therapeutics, controlling the chemical exposure, altering

### SCARY FACTS

- Of the 81 million American Baby Boomers (born between 1946 and 1964), a third are obese and an additional 36 percent are overweight. *Source: Associated Press-LifeGoesStrong.com poll August 30, 2011*
- Today, over 150 million people are suffering from diabetes worldwide while over 300 million people are estimated to be obese. As a result, up to 1.7 billion of the world's population is at increased risk. *Source: World Health Organization 2011*
- A new study predicts that if the current "obesity epidemic" continues unchecked, by 2030 50 percent of the US adult population will be clinically obese. *Source: Lancet, 378, Issue 9793, August 2011*

dietary composition rather than quantity of food and, in the morbidly obese, implantable

devices and even radical surgical interventions.

(12 and 13 percent respectively,) than among whites (7 percent).<sup>iii</sup> Furthermore, the rate is inversely proportional to household income,<sup>iv</sup> often because of this population's higher exposure to synthetic chemicals in their environment, as well as predisposing risk factors and a possible susceptibility to metabolic disruption. Obesity rates in the U.S. have risen dramatically, with more than one-third of the adult population considered to be obese.<sup>v</sup>

## 10 INTERESTING DYNAMICS IN DIABETES

1. The theory that diabetes is triggered by energy imbalance is giving way to a more nuanced understanding of the multiple trigger points of a complex condition.
2. The exposome – the sum of all internal and external chemical exposure – plays a significant role in diabetes onset.
3. Rapid weight gain, coupled with the inability to shed stored fat, is closely linked to the preponderance of environmental chemical exposures.
4. 24 genomic loci are linked to diabetes, but none are powerfully predictive.
5. High levels of certain amino acids are associated with increased risk (60-100%).
6. Poor nutrition during pregnancy may increase the number of adipocyte precursor cells, re-set insulin signaling pathways in the neonate, thus increasing risk of obesity/diabetes later.
7. Lowering glucose level, though not aggressively, is most effective in delaying/preventing the onset of cardiovascular disease when achieved soon after onset of the disease.
8. SGLT2 inhibitors appear to have a positive impact on blood glucose concentration, weight loss, blood pressure, pancreatic function, high blood triglycerides and cholesterol.
9. Anti-CD3 therapy preserves  $\beta$ -cell function, enabling nearly insulin-independent diabetics.
10. For some, gastric surgery may be required to achieve balanced -energy intake and glycemic control.

### Incidence increases

Diabetes often is considered a disease of affluence because its progression throughout the world can be correlated with the increasing wealth of nations. China is a prime example. Researchers at the China-Japan Friendship Hospital in Beijing tested some 46,000 people and concluded that 92.4 million people -- nearly 10 percent of the population of the Peoples' Republic of China -- have type 2 diabetes. That same study suggested that 148.2 million people have pre-diabetes, defined as abnormally high blood sugar levels that develop before the actual disease manifests itself. The onset of diabetes, as well as heart disease and obesity, is linked to the richer diets and reduced physical activity that accompanied China's economic gains.

In the United States, in contrast, diabetes is generally associated with low incomes and educational levels. Recent data from the Centers for Disease Control indicates that diabetes is more prevalent among self-reporting Hispanics and blacks

### Causes

Studies of the onset of diabetes traditionally have been closely linked to the theory of energy balance – essentially, over-eating and under-exercising – which leads to fat cell weight gain. That weight gain leads to metabolic stress and fatness, which leads to the insulin resistance that is the predisposing factor in the onset of type 2 diabetes. Likewise, in type 1 diabetes, the inflammatory stress of obesity amplifies the immune response, triggering disease onset<sup>vi</sup>.

The energy balance approach, however, minimizes the role of specific dietary components in energy metabolism and fuel oxidation, and overstates other

environmental factors. For example, an analysis of data from more than 630,000 children revealed that 89 percent of the children who slept less than 10 hours per night were obese<sup>vii</sup>, while those sleeping 10 hours or more tended not to be obese.

Current research, therefore, points toward metabolic perturbation, which considers the composition, rather than the quantity of food consumed.<sup>viii</sup> Poor understanding of the relative merits of various types of foods, including the differences between processed and non-processed foods, appears to be a contributory factor in obesity and the onset of diabetes. For example, although foods labels prominently list fat content, carbohydrates are given lesser emphasis on the label despite significantly contributing to the glycemic load. Or in other words, the food stuffs that cause a biological inflammation response and a metabolic disturbance are not adequately presented on processed foods.

Changes in the Finnish diet since 1972 corroborate the effect of dietary changes upon disease. The Finnish Heart Association and the Finnish Diabetes Association, working together, have launched a Heart Symbol, which appears on packaging of heart-healthy

foods, and the government launched a campaign in the early 1970s to change food consumption patterns. Since those studies began, Finns have replaced whole milk with skim or low fat milk and use low-fat margarine or oils instead of butter. Vegetable consumption has tripled.<sup>ix</sup> Consequently, fatty acid composition has changed so that the share of saturated fatty acid has decreased from 20 to 13 percent and the intake of fat has decreased from 38 to 33 percent, resulting in a 60 percent reduction in coronary mortality.

Recent research also points to a link between advanced glycation end-products (AGEs) that are used to enhance flavors in processed foods and onset of diabetes. AGEs suppress host defenses and intracellular reactive oxygen species, leading to inflammation and obesity and can contribute to beta cell dysfunction, impaired insulin secretion and insulin resistance.<sup>x</sup> Results indicate that restricting AGEs is a promising, cost-effective intervention that is broadly applicable.

Subsequent research has addressed the interactions between diet and genomics. Research now shows that fatty acids can modulate visceral fat deposition and thereby affect an

individual's predisposition for obesity and obesity-related inflammation. This knowledge may help researchers understand the variability within the obese population in response to weight gain, weight retention, diabetes onset and response to treatment. That, however, is only part of the picture. Research suggests that the many classes of fatty acids probably do not act via a single pathway.<sup>xi</sup> There is data to suggest that many different pathways may be involved.

Environmental triggers also are causative. The speed of weight gain and the inability of patients to lose weight led researchers to suspect other factors, such as chemical exposure. As researchers learn more about disease onset, their definition of environmental factors is changing. Realizing that approximately 90 percent of human disease is attributed to environmental factors<sup>xii</sup>, yet only 7 to 10 percent is attributed to occupational exposure,<sup>xiii</sup> they began considering the internal chemical environment (aka, the organism in and on our bodies, the gut, and the individual's microbiomes).

This exposome incorporates all exposures from conception onward, including not only exposure to air and water

pollution, but also to chemicals ingested through the diet, smoking, drug use, radiation, inflammation, infections, peroxidation, the gut microbiome, bacteria and pre-existing diseases, etc. Although measuring all chemical exposures currently not accessible or reduced to practice, the Centers for Disease Control and Prevention have developed assays to detect approximately 300 exposures in blood or urine. Strong associations were reported between the risk of type 2 diabetes and exposure to polychlorinated biphenal, heptachlor epoxide and other substances<sup>xiv</sup>. Exposure to a wide variety of pollutants, whether internally or externally, causes epigenomic alterations that become heritable.<sup>xv</sup> Epigenetic modifications also are caused by transient exposure to hyperglycemia, resulting in long-term changes in the chromatin structure and in gene expression, immune response, which mediate persistent metabolic characteristics.<sup>xvi</sup>

So far, most research regarding environmental triggers of disease has concentrated upon external exposure, often to chemicals regulated by the Occupational Safety and Health Administration (OSHA) and the

Environmental Protection Agency (EPA). A long list of pollutants and their effects upon disease onset has been developed. Many of these are endocrine disrupters that interfere with the action of normal hormones and, therefore, promote the development of metabolic diseases, such as type 2 diabetes. Many of the modulation pathways affected by endocrine disruption chemicals are important in energy regulation and glucose homeostasis.<sup>xvii</sup> They also appear to interfere with xenobiotic signaling, which affects drug, lipid and glucose metabolism, as well as inflammatory response. There is speculation that these xenobiotic receptors are now overwhelmed in their attempts to adjust to environmental stressors and, therefore, contribute to the onset of diabetes.

A body of research suggests that endocrine disrupting compounds also may affect adipose tissue and that additional mechanisms of regulation also may be affected, thus providing additional approaches for diabetes therapeutics or exposure interference technologies.

### Neonatal factors

Many of the roots of adult onset diabetes are established before birth and during infancy.

Changes in the mother's diet during pregnancy help program the neonate's predisposition to metabolic syndrome.<sup>xviii</sup> In other words, what the mother eats during critical periods of the pregnancy may modify the epigenome and thus re-set the baby's cellular energy homeostasis, fat cell production, and alter several key regulatory pathways. For example, poor nutrition during the first half of a pregnancy may increase the number of adipocyte precursor cells and thus re-set insulin signaling pathways. This, however, becomes a key component of metabolic syndrome only if it is followed by the child's accelerated growth rate soon after birth or if the child becomes obese. It appears that if the child is nutritionally challenged early in life, the risk of developing diabetes is dramatically increased.

### Prediction capabilities

Given the myriad causes of diabetes, developing risk profiles to more accurately predict the likelihood of disease onset can become extremely complicated. Although some 24 different genomic loci have been linked to type 2 diabetes, none improves the ability to predict onset of the disease.<sup>xix</sup> This leads to the conclusion that, although the understanding of the genetic



and molecular networks underlying metabolic disease is incomplete, it plays an important role in obesity and, therefore diabetes.

High throughput metabolic profiling, however, is revealing some promising biomarker(s) and candidate classifiers to stratify sub-groups. Metabolic diseases often are present years before they are clinically apparent as a defined phenotype. Therefore, it appears possible to identify changes in plasma metabolite concentrations, using the changes as clinical biomarkers to predict disease. In a multi-center longitudinal study<sup>xx</sup> of 6,000 individuals who were followed for decades, researchers used mass spectrometry to identify a panel of amino acids that, based upon their concentrations during fasting, predicted the development of diabetes in otherwise healthy individuals. High concentrations of five branched-chain and aromatic amino acids, in fact, elevated the risk of developing diabetes four-fold, and were detectable up to 12 years before any changes in insulin were evident. Earlier research supports the concept, noting that circulating amino acids may directly promote insulin resistance<sup>xxi</sup> and

that many different amino acids modulate insulin secretion.<sup>xxii</sup>

Although assessing the potential for the onset of diabetes through monitoring genetic polymorphisms has indicated a risk increase of 5 to 37 percent, elevated levels of amino acids are associated with a risk increase of 60 to 100 percent. Hyperaminoacidemia, therefore, appears to be a very early indicator of insulin resistance in certain sub-groups.

### Treatment options

Lifestyle modifications are strongly recommended to curb obesity, delay diabetes onset and, after onset, mitigate its effects. To be most effective, these modifications typically result in the loss of 7 to 10 percent of a patient's initial weight.<sup>xxiii</sup> This weight loss, combined with exercise, reduces the risk of developing type 2 diabetes. Pharmacotherapy also often is recommended as an adjunctive treatment.

For the morbidly obese, however, implantable devices or gastric surgical options may be required for them to achieve their target glycemic control.<sup>xxiv</sup> In these individuals, substantial weight loss markedly improves hyperglycemia and sometimes results in a remission of type 2

diabetes. It also improves obesity-related cardiovascular risk factors. Some researchers suggest that because the risk reductions are seen soon after surgery, even before the patients lose weight, the metabolic changes that occur after gastric bypass surgery are triggered by a lower insulin baseline.<sup>xxv</sup>

Glycemic control is the standard treatment for diabetics, with long-term benefit of reducing the risk of developing diabetes-related diseases.

Glycemic control, however, is not ideal. Although the degree of glucose elevation among type 2 diabetics is a key indicator of risk, lowering glucose levels is most effective in delaying or preventing the onset of cardiovascular and other diabetic-related disease for recent-onset diabetes. For those with established, long-duration diabetes, the benefits of glycemic control upon related diseases were inconclusive<sup>1</sup>.

[Food supplements](#) have been advocated as a way of reducing obesity, and are generally welcomed by patients who view them as natural or as easier than changing their diet or exercising. Their effectiveness, however, remains questionable. A recent review of clinical trials studying the effectiveness of food supplements reported insufficient



evidence of clinically significant weight loss without undue risks<sup>xxvi</sup>. But the open question remains, is it an issue of study design or ineffectiveness of the food supplements approach?

One promising preclinical research program suggests that a particular lipid may mitigate the effects of a high-fat diet and thereby lower incidence rates for diabetes. The phospholipid dilauroyl phosphatidylcholine (DLPC), when administered to metabolically challenged mice, reverses the metabolic problems typically associated with high-fat diets, substantially improving glucose homeostasis and insulin signaling<sup>xxvii</sup>.

Nearer-term, new measurement and monitoring technologies looks promising, such as [continuous glucose monitoring](#), and the eventual adoption of artificial pancreas for individuals able to deal with the technological capability. Clinical use of advanced [closed-loop insulin delivery systems](#), however, will most likely be very gradual. The likely early applications include overnight closed-loop control to prevent nocturnal hypoglycemia, and then eventually full-time use of such systems. Their current challenges include imperfect accuracy and reliability of their continuous

glucose monitoring components, the slow absorption of subcutaneously administered rapid-acting insulin analogues and inadequate control algorithms to adjust performance to account for individual variability among patients.<sup>xxviii</sup>

### Type 1 and 2 therapies

Several new drugs that are in trials now address both type 1 and type 2 diabetes and, unlike earlier therapies, target novel pathways. Dapagliflozin, being developed by Bristol-Myers Squibb and Astra Zeneca, canagliflozin by Johnson & Johnson, and a similar compound jointly developed by Boehringer Ingelheim and Lexicon Pharmaceuticals, all target the sodium-dependent glucose co-transporter 1 (SGLT2), preventing it from reabsorbing glucose in the kidney. These SGLT2 inhibitors lower blood glucose concentrations by excreting simple sugar through the urine. They also trigger weight loss, lower blood pressure, improve pancreatic function, reduce high blood triglycerides and lower cholesterol.<sup>xxix</sup> They are in clinical trials now. But the community remains very concerned about the likelihood of achieving regulatory approval with those intended use claims.

Failure seems likely to some observers.

### Type 1 therapies

The therapeutic objective for type 1 diabetes has evolved from preserving the functional capacity of the remaining beta cells to restoring the immune tolerance to target autoantigens.<sup>xxx</sup> Although the much heralded immune suppression strategies and autoantigen therapies have, so far, proved disappointing, an alternative approach seems to have some promise.

After watching the effectiveness of anti-CD3 monoclonal antibodies in oncology work, researchers theorized that some of the autoantigens within the host at disease onset remained, and could help restore self-tolerance. Therapeutic trials of two humanized Fc-engineering monoclonal anti-CD3 antibodies, teplizumab<sup>xxxi</sup> and otelixizumab<sup>xxxii</sup>, were launched. European double-blind multi-center Phase II trials indicated that the antibody preserved beta cell function, even 48 months after therapy, resulting in a significant decrease in the need to administer insulin<sup>xxxiii</sup> so that patients neared insulin independence.

## WHAT'S NEXT

**Medical Devices** Further technological innovation will have an incalculable influence on the future of obesity and diabetes epidemic including advances in miniaturization (micro and nano scale), alternative materials, novel delivery approaches, wireless communication, digital data transfer from various ubiquitous intelligent devices, as well as the human/machine interface all aligned to monitor, manage, treat, alleviate, and actually delay disease onset. Even fashion will have an impact on diabetes-related product development.

We predict that the social phenomenon of chic medical device fashion will be here soon enough, including designer monitor watches, functional jewelry, skin tattoos to interface with implantables, and other clothing accessories for a new age of "functional fashion." Companies such as PositivID, Medtronic (with their MiniMed Infusion Systems), and larger firms like Abbott, Bayer, BD, and J&J are developing such technology, acquiring novel intellectual property and compelling device prototypes, like the G-Tone watch concept.

**Diagnostics** New developments will include: permanent on-skin rapid diagnostics to monitor and alert a person of out-of-range blood chemistry levels or metabolic aberrations with new age blood sensors; targeted personalized disease diagnostics that will stratify patient populations into metabolic sub-classifications, re-characterize the clinical phenotype, and alter the clinical trials and treatment of diabetes; and theranostic tests to identify pre-diabetes, predict disease trajectories for early aggressive intervention strategies, and target generic drugs over expensive biological agents. Companies advancing new diagnostics include Seventh Sense Biosystems, SecondGenome, Tethys Bioscience, Medco Health Solutions, Quidel, and all of the next generation sequencing companies.

**Study Focus and Study Designs:** The continued and inevitable product development failures for therapeutics in the areas of obesity and diabetes control will necessitate alternative pathways forward because the economic and social burden of the epidemic will remain untenable for society and financially troubled economies. As such, a renewed focus on the primacy of economics, clinical utility, patient adherence, and demonstrated durable behavioral change will be extremely important for commercial success of products, services, and informational medicine. The enabling technology platform for this enterprise will require collaboration from diverse stakeholders, direct lay public engagement, social network media, and creative circumnavigation of the traditional regulatory pre-market hurdles to commercialization. Industry will need to figure out how to engage and leverage these new types of circumstances. For example:

- Population-based disease registries and biocollections: Both public and private collections.
- Clinical observational studies: With linked longitudinal outcomes data and self-reported data.
- Adaptive clinical designs: Real time diagnostic and device interventions with tracked outcomes data.
- Self-organization patient social networks and research protocols: Community directed studies.

unique in terms both of potency and mechanism of action. Study results showed a long-lasting, single-dose effectiveness that enabled the full reconstitution of the immune responses to unrelated antigens within two to three weeks of treatment's end. The rapid remission is attributed to a mechanism of action that targets both pathogenic T cells and T<sub>REG</sub>, making it most effective with a primed, ongoing immune response.

Although anti-CD3 therapy appears to be best-in-class, at least five other Phase II and Phase III trials indicate that it reduces insulin requirements but generally does not trigger long term disease remission.<sup>xxxiv</sup> In mice, it is most effective immediately at diagnosis. Therefore, there is speculation that a multi-pronged approach will be most effective, involving combination therapies to maintain the balance of pathogenic and regulatory pathways, drugs that target co-stimulatory pathways and consideration of the state of the pancreatic beta cell when designing therapy - thus begging the question,

This anti-CD3 approach was




who and how such combinatorial approaches will be performed and brought to market.

## Conclusion

Advances in understanding the many causes and contributing factors of type 1 and type 2 diabetes are resulting in promising approaches that include pharmacologic interventions, new diagnostics, new drug targets and new options in diet and lifestyle modification. For most, ongoing research is called for, but these many studies provide insights into new, evolving approaches to help clinicians treat new and

established cases in ways that promote desirable results in the here and now.

Because of the burden of disease, the acute economic drag placed on populations, and the overall productivity shock wave caused by this epidemic, there is a demand for new solutions and innovative life science products, socio-behavioral interventions, health literacy programs, food consumption consciousness efforts and epidemiologically driven behavior tactics to alter the trajectory of diabetes globally.

Scientia Advisors believes that the convergence of food products, drugs, devices, diagnostics, measurement science, electronic medical information, and social network theory delivered to resolve some of these immediate dilemmas described above will become a new engine of compelling life science solutions in diabetes management. 

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