Diabesity: Implications for Treatment and Drug Development

The term "diabesity" has been used to refer to the twin pandemics of type 2 diabetes (T2D) and obesity.[1] It was originally used after experiments showed that overfeeding healthy subjects to an overweight, but not obese, average body mass index (BMI) of 28 kg/m^2 led to deterioration in fasting and postprandial (after meal) glucose tolerance. We now know that this glucose intolerance is related to insulin resistance, and it can be reversed by subsequent weight loss.[2]

The latest data indicate nearly 42 percent of the U.S. population is considered obese; 49 percent has either prediabetes or T2D; and more than 90 percent of patients diagnosed with T2D are overweight or obese.[3,4] Here, we discuss the overlap in pathophysiology and treatment of diabetes and obesity, along with considerations for streamlining clinical development of treatments that have therapeutic promise for both conditions.

Insulin Resistance, Adipocytokines and Inflammation

Obesity is a condition of energy surfeit, or too much energy, and is associated with expanded and ectopic adipose tissue stores. Excess fat, particularly visceral adiposity stored in abdominal tissue surrounding the intestines and ectopic fat in the liver, is associated with elevated adipose-derived metabolites that cause local and systemic low-grade inflammation. This is reflected in elevated levels of specific cytokines that are clearly associated with decreases in insulin action – specifically, insulin resistance, a hallmark phenomenon of diabesity that leads to a complex cascade of metabolic adjustments to physiologic stress, which in many individuals leads to eventual T2D.[5]

T2D occurs when insulin resistance (initially with compensatory insulin hypersecretion) and impaired insulin secretion (initially from pancreatic lipotoxicity, later from beta-cell loss due to inflammation, and other mechanisms) lead to loss of glucose homeostasis and frank hyperglycemia. Many people still think of T2D as a problem of "too much sugar," but it has been established that T2D is more accurately thought of as a lipid disorder.[6,7] The risk of lipotoxicity is increased in obese individuals where excess triglyceride handling – due to over-ingestion (eating) or production (de novo lipogenesis) – results in accumulation of toxic lipid metabolic by-products. Lipotoxicity in the liver is a proximate cause of both fatty liver and hepatic insulin resistance, which together contribute to the risk of T2D.

Notably, not all patients treated for obesity may develop diabetes, and not all patients with T2D or pre-diabetes are obese. For example, there are significant portions of south-east Asian populations with insulin resistance, fatty liver and pre-diabetes who do not meet western obesity BMI criteria.

Treating Diabesity

The complex interdependent metabolic and immune changes associated with both obesity and T2D – including those leading to insulin resistance and inflammation, such as adipocytokine and endocrine activity – contribute to the pathophysiology of diabesity. However, they have also shown relevant treatment efficacy.

For example, leptin is an adipocytokine that is a master controller of energy balance. As an adipose-derived hormone, leptin sends signals to the brain about the adequacy of energy (adipose) stores, but it also affects immune function and inflammation through a type 1 cytokine receptor.[8] Obesity is associated with leptin resistance, and elevated leptin concentrations may support dysfunctional adipogenesis and inflammation in the setting of obesity.[9] Leptin analogs have shown dramatic therapeutic potential, but only in rare and extreme forms of obesity and hyperinsulinemic diabetes associated with lipodystrophy.[10]

Gut-derived, so-called "incretin" hormones, such as glucagon-like peptide-1 (GLP-1), play an important role in modulating normal glucose-stimulated insulin responses. In T2D, a reduction in secretion or sensitivity to incretin hormones contributes to hyperglycemia. Treatment with exogenous GLP-1 analogs can normalise hyperglycemia in T2D. The use of GLP-1 has also proven effective in obesity treatment, due to central effects on appetite and ingestion regulation. Large outcomes trials in T2D and obesity have shown that GLP-1 agonists can improve overall mortality and specific outcomes related to atherosclerosis, and cardiac and kidney failure.

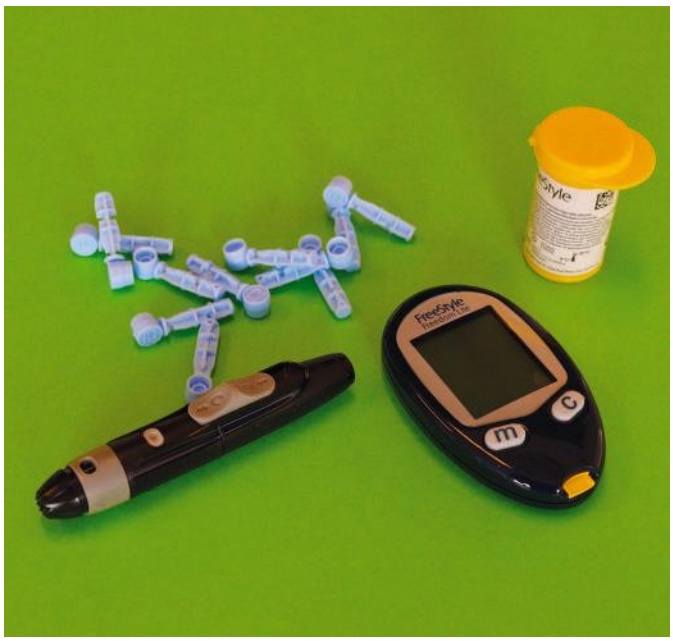
Weight loss through diet and lifestyle alone can improve or resolve insulin resistance and decrease inflammatory markers. However, one of the most effective types of insulin sensitiser agent, PPAR-gamma agonists, led to significant improvements in glycemia in people with T2D, but actually caused weight gain due to additional adiposity.

Newer "diabesity" agents in early in clinical development, for example agents that modulate abnormal lipid availability or function, and/or directly affect the various mechanisms of insulin resistance, including anti-inflammation, should be considered for both potential obesity and T2D indications. Developers should pay careful attention to mechanisms of action and potential effects in early translational clinical development to best plan for sequential, parallel or milestone-based integrated full clinical development plans.

Clinical Trial Design Considerations for Diabesity Therapies

Traditional clinical development challenges are of increased importance for therapies for chronic use in widespread conditions of public-health magnitude, such as diabesity. One such challenge is recruitment and retention. Broader participation can be achieved by approaches such as using active comparators in weight loss trials, reducing study burden using hybrid decentralisation for randomisation and limiting the number of in-clinic visits. Additionally, new regulatory guidelines mandate broader inclusion and diversity, and safety data for at least two years. So sponsors must avoid, for example, over-representation of middle aged women in obesity trials or white males in T2D studies.

Engagement and retention are particular challenges for long-term clinical trials. To mitigate these challenges, sponsors can utilize proactive measures, such as patient education on the investigational product, proactive provisions for investigational product restart after temporary discontinuation, and a dedicated retention team. With these and other methods, ICON was able to support a successful large



cardiac outcomes trial for GLP-1 receptor agonists, with over 9900 subjects with T2D followed for up to seven years, attaining greater than 97 percent completion rate.

Based on the recent approvals for GLP-1 receptor agonists for obesity in addition to T2D, integrated approaches to early and late clinical development for new "diabesity" agents can now be considered. There is growing interest in the simultaneous development of assets not just for diabetes and obesity, but also for pre-morbid conditions — such as prediabetes and steatosis (fatty liver) — with potentially more public health impact but currently without approved regulatory registrational pathways. Given the broader range of potential patients suitable to study and the currently separate indications to be treated, ICON is exploring potential advantages to innovative uses of master protocols, which are constructed to test multiple hypotheses with an overarching set of procedures intended to improve efficiency. This maximises the ability to identify relevant populations at screening and to direct them to appropriate sub-studies.

The Future of Diabesity Treatment

The emerging understanding of shared pathophysiology, morbidity and mortality of obesity and T2D, as well as the demonstration of beneficial efficacy and outcomes of GLP-1 agonists, is stimulating research for more therapies to address diabesity-related indications. These include obesity and diabetes and their shared complications, but also the possibility to pursue new indications for pre-morbid conditions such as pre-diabetes and fatty liver. Therefore, pipeline programs that target lipotoxicity and inflammation, or leverage adipose or intestinal hormones to modulate energy intake and expenditure, or use other approaches, including microbiome modification, will all increasingly benefit from early clinical development planning that considers how best to learn – and to demonstrate data supporting – the role of newer potential assets across multiple indications.

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Dr. Bruce, MD joined ICON in May 2021. He has over 22 years of experience working in clinical research or pharmaceutical industry with broad experience across all phases of clinical development and responsible for clinical development strategy and execution from pre-IND to first-in-human and Phase I/II proof-of-concept trials through Phase III planning, execution and filing and Phase IV support. His focus is in Diabetes/Metabolism and Cardiovascular therapies. He has a long history of leading clinical development teams and functions, providing oversight of transition from translational Proof-of-Concept to full development, and shepherding programs through internal portfolio review in large pharma and medium sized biotech.

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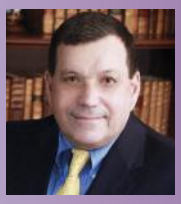

Dr. Martin, MD, FACC is board certified in Cardiovascular Diseases and Interventional Cardiology. He has over 35 years of clinical practice and investigational experience. Jack is an experienced consultant for pharmaceutical and medical device companies. This includes all phases of product development including device design, trial design, FDA pre-sub and panel meetings. Dr. Martin has served as study chairman or the coordinating investigator for multiple multicenter international pharmaceutical and device trials. His previous roles included Assistant Professor of Medicine, University of Pennsylvania School of Medicine, Philadelphia, Chief, Division of Cardiovascular Diseases and Chief of Interventional Cardiology, Health System. He has served as President and a Board Member of several research foundations and is a respected educator having served as an Interventional Cardiology Fellowship Program Director. He has numerous peer-reviewed publications, is an active journal reviewer and has been a frequent invited speaker at national and international professional conferences. While at ICON, Jack has provided medical oversight for numerous cardiometabolic studies and has focused on cross functional team building to provide novel solutions for the effective delivery of drug and device trials.