The Impact of Prediabetes on Early Clinical Metabolic Disease Studies

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The New Normal

A recent trend in clinical study design is to incorporate patients earlier in drug development. Along with elements of proof-of-concept and pharmacodynamic endpoints, this can facilitate the detection of early efficacy signals in a population of interest. For chronic metabolic disease indications such as type 2 diabetes, obesity and nonalcoholic steatohepatitis (NASH), there is a shift in inclusion criteria from healthy normal subjects to patient groups in early drug development, with these clinical studies benefitting from the enrollment of prediabetes subjects.

The Prediabetes State

Prediabetes describes a state of glucose impairment which holds a significant risk of developing type 2 diabetes. It is estimated that 1 in 3 Americans have prediabetes, yet only 1 out of 10 individuals are aware of their condition [1]. Indeed, the national average is similar to what we observed during our community outreach events where we offer free prediabetes screening [2]. Risk factors for prediabetes include being overweight or obese, 45 years of age or older, a family history of type 2 diabetes, a sedentary lifestyle, and previously having gestational diabetes [1]. There is also an ethnicity component to prediabetes prevalence where genetic, environmental and social-economic factors can contribute to the incidence of prediabetes in minority populations.

According to the American Diabetes Association (ADA), prediabetes can be diagnosed by one of three ways [3]:

_ Fasting plasma glucose of 100 - 125 mg/dL (5.6 – 6.9 mmol/l)
_ 2-hour oral glucose tolerance test value of 140 - 199 mg/dL (7.8 – 11.0 mmol/l)
_ Hemoglobin A1c (HbA1c) of 5.7 - 6.4% (39 – 47 mmol/mol)

A prediabetes state typically manifests as elevated fasting glucose with greater impairment in postprandial glucose (Figure 1). In addition, insulin response is increased during prediabetes, as observed by the amount of insulin secreted from the pancreas in reaction to circulating glucose levels. This upregulation of insulin secretion is a compensatory response to maintain near normal glucose concentrations. In parallel, insulin resistance occurs at the level of the skeletal muscle, adipose tissue, liver and other insulin-sensitive tissues [4]. Insulin resistance refers to the inability of insulin to induce a signaling response within a given cell, which can lead to further elevations in fasting and postprandial glucose levels, ultimately leading to type 2 diabetes if left unchecked.

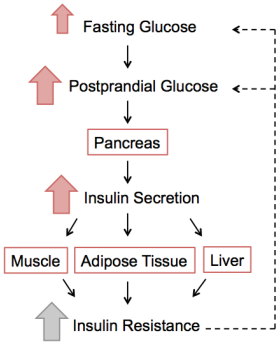

Figure 1.
Insulin resistance contributes to elevated fasting and postprandial glucose levels in prediabetes. Insulin secretion is increased in response to higher glucose levels, yet this compensation is not enough to achieve normal glucose concentrations.

Glycemic Functional Assays

The oral glucose tolerance test (OGTT) is considered the gold standard for diagnosing diabetes and prediabetes. Briefly, plasma glucose and insulin are measured before and during a 2-hour period following the consumption of a glucose drink (75 g anhydrous glucose). This diagnostic test can also provide valuable pharmacodynamic insight into a drug's efficacy. Change in the area-under the curve as well as computational indices (insulinogenic index, insulin secretion index, disposition index) calculated from the OGTT results can reveal an effect on β-cell function, as well as skeletal muscle, hepatic and whole-body insulin sensitivity. These indices are similar to those obtained during a clamp however, this procedure is far less invasive [5]. When a mixed meal is substituted for the glucose drink, the induction of entero-insular axis allows for the evaluation of gut hormones, incretins and other metabolic factors that respond to a meal challenge. We have previously shown the mixed meal tolerance test (MMTT) to a robust assay with strong repeatability [6]. To evaluate a drug's effect on glucose levels throughout the day, continuous glucose monitoring (CGM) provides blood glucose readings every 5 minutes and implanted sensors can be worn for up to 14 days. CGM is a minimally-invasive approach to intensive glucose tracking and has been coined the "ECG Holter-monitor for glycemia" [7]. Anti-diabetes medication as well as weight loss products and anti-NASH drugs which improve glycemia and/or insulin sensitivity are anticipated to show meaningful change in OGTT, MMTT and CGM results in both prediabetes and type 2 diabetes subjects, and these functional assays can be informative pharmacodynamic endpoints.

Prediabetes and Early Clinical Drug Development

Type 2 Diabetes: Study endpoints for the anti-diabetes therapies include a clinically significant improvement in HbA1c. HbA1c is an indicator of long-term glucose control over the past 2-3 months and is appropriate for interventions ≥12 weeks [8, 9]. For shorter

studies, endpoints may include a change in glycated fructosamine, fasting plasma glucose, postprandial glucose or 24-hour mean weighted glucose. A major safety concern with diabetes patients during a clinical study is the risk of glucose excursion. To this end, all cases of hyperglycemia and hypoglycemia must be documented, and rescue thresholds as well as glycemic-specific stopping rules ought to be outlined in the study protocol [8, 9]. Diabetes patients may be especially vulnerable during placebo-controlled studies, monotherapy studies or during washout periods. Since prediabetes subjects maintain a degree of glucose control, they are less likely to experience severe glucose excursions than type 2 diabetes subjects. Therefore, the enrollment of prediabetes subjects in a clinical study with a glucose lowering agent is one strategy to mitigate glycemic risk while gaining valuable information on dose ranges and drug efficacy.

Weight Management: Obesity is defined as body mass index (BMI) value of ≥30 kg/m^2 and is associated with excess fat mass. It has been shown that depot-specificity plays an important role in the development of chronic metabolic diseases, where accumulation of belly fat (visceral adipose tissue) is associated with a low-grade chronic state of inflammation and is an underlying risk factor for metabolic syndrome, type 2 diabetes and NASH [10]. Weight loss can be a mechanism for type 2 diabetes treatment [8] or an indication on its own [11]. For efficacy studies, weight management inclusion criteria should consist of subjects with a BMI ≥30 kg/m^2 or ≥27 kg/m^2 if accompanied by comorbidities such as type 2 diabetes, hypertension, dyslipidemia, sleep apnea and/or cardiovascular disease. In addition, before commencing late phase studies, dose-response profiles and pharmacokinetic properties must be well described in subjects with a range of BMIs since adiposity may influence drug disposition [11]. This population of overweight/obese but otherwise healthy subjects will likely fall within the prediabetes classification since an estimated 80% of subjects with glucose impairment are overweight or obese [12].

Nonalcoholic Steatohepatitis: NASH can lead to liver cirrhosis, end-stage liver failure and even hepatocellular carcinoma. Liver fat accumulation, inflammation and hepatic cellular injury are the hallmarks of steatohepatitis [13]. NASH is recognized as the second leading indication for liver transplant [14]. There is no FDA-approved treatment for NASH and no guidelines regarding this indication have been released by regulatory agencies [15]. Current Phase III endpoints include the histological assessment of steatohepatitis resolution without worsening of fibrosis and an improvement of fibrosis stage with no worsening in steatohepatitis. For early clinical studies, endpoints include a change in liver fat content and reduction of hepatic inflammation. These measurements can be determined by imaging techniques like magnetic resonances imaging (MRI) and elastography (MRE) or velocity-controlled transient elastography (VCTE). While obese subjects may display a fatty liver only, prediabetes subjects are more likely to possess inflammatory and fibrotic elements of the disease. Indeed, prediabetes was found to be independently associated with hepatic inflammation and fibrosis in NAFLD subjects [16]. In addition, these imaging modalities are sensitive to body habitus; VCTE is influenced by skin to (liver) capsule distance [17] and morbidly obese subjects may not conform to MRI and MRE instrument specifications [18], therefore for technical reasons a (overweight) prediabetes cohort may be more apt for early NASH studies.

Is Prediabetes an Indication?

Currently, diet and exercise are recommended for the treatment of prediabetes. However, Standards of Care indicate that some prediabetes patients may benefit from off-label use of metformin [19], the first-in-therapy anti-diabetes medication. Furthermore, pharmaceutical developers of other diabetes drug classes are examining long-term outcome data in order to support the use of their therapies in the prevention or delay of type 2 diabetes. The European Medicine Agency (EMA) recognizes that this a challenging undertaking due to the long progression of the disease, and therefore released a concept paper in 2016 to address the ongoing need for diabetes prevention [20]. This may result in a change to current guidelines to accelerate the approval process for prediabetes labelling.

Summary

In early clinical drug development, prediabetes subject enrollment holds a number of advantages over type 2 diabetes patients. Opposed to full-blown type 2 diabetes patients, prediabetes subjects tend to have normal ECG and clinical lab values. Furthermore, type 2 diabetes subjects often express an unwillingness to be on additional medication or have concerns over losing glycemic control while taking an investigation product [21, 22]. On the other hand, prediabetes subjects are typically drug naïve or on minimal medications, and this may be advantageous for Phase I studies where concomitant medication is usually exclusionary. Moreover, prediabetes subjects are characterized as insulin resistant, yet they maintain a degree of β-cell function with adequate insulin secretion from the pancreas. This is an important consideration during dose escalation studies for glucose-lowering agents. In addition, signals of improved insulin sensitivity through OGTT, MMTT or CGM can be obtained in prediabetes subjects just as there are in type 2 diabetes subjects. In summary, prediabetes subject enrollment in early clinical studies for chronic metabolic diseases offers an opportunity to examine pharmacodynamic endpoints in a population of interest while minimizing safety concerns typically observed with diabetes patient studies.

Celerion is committed to raising prediabetes awareness and offers free HbA1c screening during community outreach events and in our clinics. Through this initiative, we provide vital education on prediabetes risk and offer ADA resources on diabetes prevention.

Questions? Contact Sabina Paglialunga at:
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