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DIVISION OF DIABETES, LIPID DISORDERS AND OBESITY
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CLINICAL CONSULTATION

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SUBJECT: Criteria for the diagnosis of type 2 diabetes and valid surrogate endpoints for increased risk of type 2 diabetes.

DATE CONSULT RECEIVED: June 6, 2023

DATE CONSULT COMPLETED: January 31, 2024

A. Background

The CFSAN consult states that "In 2012, CDER/DMEP[1] provided a consultation to CFSAN/ONFL on valid surrogate endpoints for type 2 diabetes in support of a qualified health claim on the relationship between the consumption of whole grains and a reduction in risk of type 2 diabetes." In that consult, DMEP discussed the following surrogate endpoints for increased risk of type 2 diabetes:

1) elevated or abnormally high blood glucose levels (fasting blood sugar of > 100 mg/dL and < 126 mg/dL) is the definition of impaired fasting glucose which is associated with an increased risk for the development of diabetes

2) an oral glucose tolerance test (OGTT) of greater than 140 to less than 200 mg/dL is the definition of impaired glucose tolerance which is also associated with an increased risk for the development of diabetes

3) insulin resistance, which is assessed by various measurements of insulin sensitivity, including glycemic clamp method, homeostasis model assessment, and fasting insulin/glucose ratio is associated with an increased risk for diabetes

The above surrogate endpoints were used in the evaluation of several qualified health claims, including whole grains (2013), psyllium husk (2014) and high amylose maize starch (2016).

In April 2020, following the receipt of a qualified health claim petition on the relationship between the consumption of yogurt and a reduction in the risk of type 2 diabetes, CFSAN/ONFL consulted CDER/DDLO to obtain clarification regarding the current diagnostic criteria for type 2 diabetes and "updated valid surrogate endpoints for risk of type 2 diabetes" (1).

CFSAN/ONFL is now consulting CDER/DDLO regarding the current diagnostic criteria for type 2 diabetes and "updated valid surrogate endpoints for risk of type 2 diabetes" to be used more broadly for health claim and qualified health claim petitions on type 2 diabetes.

B. Consult Questions:

1. *Criteria for Diagnosis of Type 2 Diabetes*

    a. *What are the current criteria for diagnosis of type 2 diabetes?*

DDLO Response: According to the American Diabetes Association (ADA) Standards of Medical Care (2), the diagnostic criteria for diabetes are shown in **Table 1**.

[1] DMEP is the Division of Metabolism and Endocrine Products. Diabetes products are now regulated by the Division of Diabetes, Lipid Disorders and Obesity (DDLO) following Office of New Drugs (OND) re-organization in 2020.

Table 1: Criteria for the diagnosis of diabetes

A. Fasting plasma glucose (FPG) ≥ 126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 hours. *
   OR
B. 2-hour plasma glucose (2-hr PG) ≥ 200 mg/dL (11.1 mmol/L) during oral glucose tolerance test (OGTT). The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*
   OR
C. HbA1c ≥6.5% (48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP[2] certified and standardized to the Diabetes Control and Complications Trial (DCCT) assay.*
   OR
D. In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).

** In the absence of unequivocal hyperglycemia, diagnosis requires two abnormal test results from the same sample or in two separate test samples.*

Type 2 diabetes is the most common form of diabetes (accounting for 90 to 95% of all diabetes). Clinical risk factors for type 2 diabetes include but are not limited to increasing age, obesity, physical inactivity, first degree relative with diabetes, certain race/ethnic subgroups (African American, American Indian, Hispanic, Latino, Asian American), dyslipidemia, history of gestational diabetes, and insulin resistance. **A clinical diagnosis of type 2 diabetes is typically based on the standard diabetes diagnostic criteria (Table 1) along with the presence of known type 2 diabetes risk factors** (2)**.**

Due to variability in the measurements of glucose metabolism, two measurements are required in any given individual in the absence of classic symptoms to make a diagnosis of diabetes and initiate treatment (2).

The diagnosis of diabetes is made based on biomarkers that indicate elevated blood sugar concentration in the diabetic range (e.g., elevated fasting blood glucose ≥ 126 mg/dL or 7 mmol/L, elevated 2-hour glucose ≥ 200 mg/dL or 11.1 mmol/L following 75-g OGTT, or elevated hemoglobin A1c ≥ 6.5%) and is not made based on clinical outcomes such as development of diabetic complications. To be clear, the above values for the specified parameters constitute criteria diagnostic for diabetes mellitus, not surrogate endpoints for diabetes or for predicting a risk of diabetes.

b. Is it appropriate to ascertain the incidence of type 2 diabetes based on one parameter? Or would it depend on the specific parameter? For example, fasting plasma glucose versus random plasma glucose.

DDLO Response: Yes, it may be appropriate to diagnose type 2 diabetes on a single parameter, depending on the clinical scenario and specific parameter. According to ADA guidelines, the main

[2] NGSP, the National Glycohemoglobin Standardization Program.

parameters used in the diagnosis of diabetes include FPG, 2-hr PG after 75-gram OGTT, and HbA1c. If there is unequivocal hyperglycemia, the diagnosis can be based on a single measurement of any one of these parameters. In the absence of unequivocal hyperglycemia, the diagnosis requires two abnormal test results from the same sample (for example, abnormal FPG and HbA1c) or in two separate samples (for example, two abnormal FPGs). In the latter example (i.e., two separate samples), if the measurement is near the margins of the diagnostic threshold, repeating the test in 3-6 months should be considered, given the known variability in blood glucose measurements (2). Thus, a single parameter may be used, if at least two measurements are obtained or if the result of a single measurement indicates unequivocal hyperglycemia. Random plasma glucose is not felt to be as specific for diabetes compared to the other listed parameters and for this reason it is only to be used as a diagnostic criterion along with classic symptoms of hyperglycemia or hyperglycemic crisis.

2. *Valid Surrogate Endpoints for Type 2 Diabetes*

Are the surrogate endpoints listed in the 2012 CDER/DMEP consult still valid and accurate for assessing the risk of developing type 2 diabetes?

DDLO Response:
Background: As discussed in FDA's 2009 guidance for industry on the scientific evaluation of health claims[3], a surrogate endpoint for disease risk is a biomarker that has been shown to be a valid predictor of disease risk and may be used in place of clinical measurements of the onset of the disease in a clinical trial. The guidance cites "elevated blood sugar concentrations and insulin resistance" as examples of surrogate endpoints for risk of type 2 diabetes accepted by the National Institutes of Health and/or CDER.

The 2012 CDER/DMEP consult mentions the following proposed surrogate endpoints for risk of type 2 diabetes: 1) elevated or abnormally high blood glucose levels (fasting blood sugar of > 100 mg/dL and < 126 mg/dL), 2) OGTT of greater than 140 to less than 200 mg/dL, and 3) insulin resistance, assessed by various measurements of insulin sensitivity. It does not address the validity of the proposed surrogate endpoints, other than a statement that the endpoints "were appropriate."

DDLO clarification regarding the proposed surrogate endpoints listed in the 2012 CDER/DEMP consult:
Epidemiological studies have shown that individuals with elevated blood sugar concentrations that do not meet criteria for diabetes but are still too high to be considered normal have increased risk of developing type 2 diabetes, and may be considered to have "prediabetes." The ADA has proposed three laboratory criteria to define prediabetes (2). DDLO therefore considers elevated blood sugar concentrations consistent with these diagnostic criteria for prediabetes to constitute valid and accurate surrogate endpoints for increased risk of type 2 diabetes (see **Table 2**).

[3] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-industry-evidence-based-review-system-scientific-evaluation-health-claims.

Table 2: Criteria to define prediabetes (adapted from ADA Standards of Medical Care, 2022)

a) Impaired fasting glucose, defined as FPG 100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L)[4]
   OR
b) Impaired glucose tolerance, defined as 2-hr PG during 75-gram OGTT of 140 mg/dL (7.8 mmol/L) to 199 mg/dL (11.0 mmol/L)
   OR
c) HbA1c 5.7 to 6.4% (39-47 mmol/mol)

For all three tests, the degree of risk of diabetes is proportionate to the measured value, with more moderate risk at the lower limit of the range that denotes risk and greater risk at the higher end of the range that denotes risk.

DDLO notes that insulin resistance may often accompany elevated blood sugar concentrations meeting diagnostic criteria for prediabetes. However, DDLO does not consider insulin resistance in the absence of elevated blood sugar to constitute a valid and accurate surrogate for risk of type 2 diabetes. Although insulin resistance has long been associated with increased risk of developing type 2 diabetes, insulin resistance alone is insufficient to produce type 2 diabetes. Type 2 diabetes is the result of two major defects: 1) impaired pancreatic β cell function leading to relative (rather than absolute) insulin deficiency, and 2) insulin resistance (2). While insulin resistance can initially be compensated for by increased β cell secretion of insulin, progressive β cell failure leads to impaired glucose homeostasis and eventual type 2 diabetes (3). Many individuals with obesity and insulin resistance may never develop type 2 diabetes if they do not develop β cell dysfunction (4). Once present, β cell dysfunction results in impaired glucose homeostasis which can be measured directly by blood glucose laboratory criteria. Thus, insulin resistance alone cannot be relied on to predict a meaningful risk for the development of type 2 diabetes itself.

It is important to note that impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) represent different metabolic defects. IFG is the result of abnormalities in both basal insulin secretion and hepatic insulin sensitivity to control hepatic glucose output in the fasting state. In contrast, IGT represents impaired physiologic response to a carbohydrate load, which requires prompt increase in insulin secretion as well as adequate hepatic and muscle insulin sensitivity (5). Risk of diabetes appears to be greatest in individuals with combined IFG and IGT when compared to those with isolated IFG or IGT (6). Similar to the glucose measures (IFG and IGT), several prospective studies have demonstrated a strong continuous association between HbA1c in the prediabetic range and subsequent type 2 diabetes (7).

Insulin sensitivity/resistance[5] can be directly measured via several methods, including the hyperinsulinemic euglycemic clamp (considered to be the "gold standard" test), and the intravenous glucose tolerance test. As direct methods can be invasive and complicated to perform, indices of insulin

[4] The World Health Organization and other diabetes organizations define impaired fasting glucose cutoff at 110 mg/dL (6.1 mmol/L).

[5] Some of these indices estimate 'insulin sensitivity' (e.g., Matsuda index). Lower insulin sensitivity correlates to higher insulin resistance.

resistance are often calculated using fasting insulin and glucose or in combination with insulin and glucose levels obtained during an oral glucose tolerance test. Among the indices of insulin resistance, homeostatic model assessment (HOMA-IR) and quantitative insulin sensitivity check index (QUICKI) (both derived from fasting measurements) are widely used measurements of insulin resistance. However other indices including Matsuda index, $SI_{IS}OGTT$, and Avignon's SiM, have been shown to correlate strongly with hyperinsulinemic euglycemic clamp results (8) and in our view would be acceptable measures of insulin sensitivity/resistance, when used in combination with the prediabetic criteria discussed above, for health claim evaluations.

In summary, for the purposes of health claim evaluations[6], DDLO recommends the following surrogate endpoints for increased risk of type 2 diabetes:

- Prediabetic criteria
  - Impaired fasting glucose, defined as fasting plasma glucose 100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L)
    OR
  - Impaired glucose tolerance, defined as 2-hr plasma glucose during 75-gram oral glucose tolerance test of 140 mg/dL (7.8 mmol/L) to 199 mg/dL (11.0 mmol/L)
    OR
  - HbA1c 5.7 to 6.4% (39-47 mmol/mol)

DDLO currently does not recommend the use of insulin resistance as an independent surrogate endpoint for increased risk of type 2 diabetes in health claim evaluations. However, DDLO believes that insulin resistance in the context of elevated blood sugar concentrations meeting the prediabetic criteria listed above would strengthen the accuracy and validity of the use of specified elevated blood sugar concentrations as a surrogate for increased type 2 diabetes risk. If used in that context, insulin resistance may be measured directly (hyperinsulinemic euglycemic clamp, intravenous glucose tolerance test) or estimated using indices (HOMA-R, QUIKI, Matsuda index, $SI_{IS}OGTT$, Avignon's SiM and others) (8).

3. Acute versus Chronic Exposure

Are studies involving acute exposure (i.e., less than 1 day) to a substance (food or food component) too short to support a relationship between the substance and a reduced risk of type 2 diabetes?

[6] Note that CDER has not approved any drug or biological products to reduce the risk of type 2 diabetes. CDER's recommendations in this consult reflect the current state of the science, but we note that this consult is for purposes of evaluating health claim and qualified health claim petitions. For purposes of drug or biologic development, CDER would have to make a case-by-case determination on the acceptability of a specific surrogate endpoint in the context of an individual development program.

DDLO Response:

Background: The FDA's 2009 guidance for industry on the scientific evaluation of health claims states the following regarding the duration of studies:

> *"Studies that use a surrogate endpoint should be conducted long enough to ensure that any change in the endpoint is in response to the dietary intervention. If the study is run for a short time period such that the effects of the substance cannot be evaluated, then scientific conclusions cannot be drawn about the relationship between the substance and the disease, and, therefore, the agency does not intend to use such a study to evaluate the substance/disease relationship. For example, FDA has considered 3 weeks to be the minimum duration for evaluating the effect of an intervention with various saturated fats on serum LDL cholesterol concentration."*

In the 2012 CDER/DMEP consult, CFSAN inquired whether scientific conclusions can be drawn regarding a reduction in type 2 diabetes risk from "acute" studies involving the assessment of glucose metabolism following the ingestion of a test meal containing the dietary intervention[7]. DMEP concluded while these studies appeared methodologically adequate, in each case, the study duration was too short to draw any conclusion regarding reduction in type 2 diabetes risk. CFSAN has since excluded studies involving "acute" exposures to dietary interventions (i.e., less than 1 day) in the evaluation of qualified health claims for reduction in type 2 diabetes risk.

***DDLO clarification regarding the duration of studies to evaluate the relationship between a substance and type 2 diabetes*:**

DDLO agrees that studies designed to evaluate changes in glucose metabolism following "acute" exposures (e.g., ingestion of a test meal containing the dietary intervention) are likely too short to draw any conclusions regarding the long-term risk of type 2 diabetes in health claim evaluations. We also note that the choice of surrogate endpoint may impact the overall duration of exposure required. For example, studies that utilize HbA1c as the surrogate endpoint may need a longer duration of exposure as compared to those that utilize plasma glucose because HbA1c reflects the average glycemia over approximately 3 months. However, the precise minimum duration of exposure to a dietary intervention that would translate into a reduced risk for diabetes is unknown.

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[7] According to the 2012 CDER/DMEP consult, these "acute" studies involved a crossover or Latin square design, in which whole grain test meals (e.g., oat bread or whole grain rye bread or flakes) or a control (glucose solution or white bread) were given for breakfast and blood was taken at fasting and after the meal (up to 2 hours) and serum glucose, insulin and areas under the curve were measured. In other "acute" studies, the whole grain test meal was given for an evening meal and then after a standard breakfast, blood was taken both at fasting and postprandial (up to 2 hours).

C. References

1. DDLO Clinical Consultation to CFSAN dated July 7, 2020, regarding valid surrogate endpoints and criteria for the diagnosis of type 2 diabetes, to be used in the evaluation of a health claim petition received by CFSAN on the relationship between yoghurt consumption and reduced risk of diabetes.
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8. Lorenzo, C., S. M. Haffner, A. Stancakova and M. Laakso (2010). "Relation of direct and surrogate measures of insulin resistance to cardiovascular risk factors in nondiabetic finnish offspring of type 2 diabetic individuals." J Clin Endocrinol Metab 95(11): 5082-5090.