FDA Center for Drug Evaluation and Research
DIVISION OF DIABETES, LIPID DISORDERS AND OBESITY
10903 NEW HAMPSHIRE AVENUE, BLDG 22, SILVER SPRING, MARYLAND 20993

CLINICAL CONSULTATION

FROM: Kim Shimy, MD
Clinical Reviewer
Division of Diabetes, Lipid Disorders and Obesity (DDLO)

Kim J. Shimy -S
Digitally signed by Kim J. Shimy -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Kim J. Shimy -S, 0.9.2342.19200300.100.1.1=2002889779
Date: 2020.07.07 14:26:13 -04'00'

THROUGH: Patrick Archdeacon, MD
Acting Associate Director, DDLO
Lisa Yanoff, MD
Director, DDLO

Lisa B. Yanoff -S
Digitally signed by Lisa B. Yanoff -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Lisa B. Yanoff -S, 0.9.2342.19200300.100.1.1=001539368
Date: 2020.07.07 14:29:49 -04'00'

TO: Fabiana Moura, PhD
Scientific Reviewer
Nutrition Programs
Center for Food Safety and Applied Nutrition (CFSAN)
Office of Nutrition and Food Labeling (ONFL)

SUBJECT: 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 yogurt consumption and reduced risk of diabetes

DATE CONSULT RECEIVED: April 20th, 2020

DATE CONSULT COMPLETED: July 7th, 2020

A. Background

The CFSAN consult states that "In 2012, CDER/DMEP[1] provided a consultation to CFSAN/ONFL on the 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 recommended the following surrogate endpoints for type 2 diabetes risk:

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

CFSAN/ONFL is currently reviewing a qualified health claim, received from Danone North America (Docket No. FDA-2019-P-1594), on the relationship between the consumption of yogurt and a reduction in the risk of type 2 diabetes. CFSAN/ONFL is consulting CDER/DDLO to obtain clarification on the current diagnostic criteria for type 2 diabetes and "updated valid surrogate endpoints for risk of type 2 diabetes".

B. Consult Questions:

Criteria for Diagnosis of Type 2 Diabetes

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

DDLO Response: According to the American Diabetes Association (ADA) Standards of Medical Care (1), 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) $\geq$ 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) $\geq$ 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 $\geq$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 $\geq$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** (1)**.**

Due to pre-analytic and analytic 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 (1).

2. *Some scientific articles indicate that the incidence of type 2 diabetes could have been based on one parameter (e.g., fasting blood glucose or random plasma glucose, etc.).*

   a) *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.*

[2] NGSP, the National Glycohemoglobin Standardization Program.

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 parameters used in the diagnosis of diabetes include FPG, 2-hr PG after 75-gram OGTT, and HbA1c. If there is unequivocal hyperglycemia (typically indicated by clinical signs and symptoms of hyperglycemia such as polyuria, polydipsia, weight loss, or hyperglycemic crisis), 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 results from the same sample (for example, abnormal FPG and HbA1c) or in two separate samples (for example, 2 abnormal FPG). 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 (1). Thus, a single parameter may be used, if at least two measurements are obtained. 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.

b) *Below are some examples of the criteria encountered in the scientific literature that evaluates the relationship between yogurt consumption and risk reduction of type 2 diabetes. Are the following criteria appropriate to ascertain the incidence of type 2 diabetes?*

   Incidence of type 2 diabetes ascertained by:

   - *Reported use of an oral hypoglycemic drug or insulin, or the first incident measurement of fasting plasma glucose ≥ 7 mmol/L (≥ 126 mg/dL).*
   - *Fasting plasma glucose ≥ 7 mmol/L (≥ 126 mg/dL) or 2-hr plasma glucose ≥ 11.1 mmol/L (200 mg/dL) after a 75-g oral glucose load.*
   - *Meeting at least one of the four criteria: fasting plasma glucose ≥ 7 mmol/L, random plasma glucose ≥ 11.1 mmol/L, use of anti-diabetes medication, and/or following dietary guidelines for type 2 diabetes.*

DDLO Response: None of the provided examples strictly satisfy the ADA standard diagnostic criteria for diabetes for a given individual (as described in Table 1). Specific comments on each example are below:

"Reported use of an oral hypoglycemic drug or insulin, or the first incident measurement of fasting plasma glucose ≥ 7 mmol/L (≥ 126 mg/dL)."

The blood glucose cutoff used in this example is the proper cutoff for a diagnosis of diabetes. However, a single abnormal FPG result can only be used to diagnose diabetes if there is clinical evidence of hyperglycemia; otherwise 2 abnormal results are required. Therefore, we recommend that you review the methodology of the literature to see how many measurements were made. The statement of 'first incident measurement' implies that only one measurement

was taken, or if more than one was taken, if the second was below the cutoff of 126 mg/dL, the subject was still considered to have diabetes which would not be accurate.

The diagnosis of type 2 diabetes could potentially be inferred by the use of an oral hypoglycemic drug that is approved only for the treatment of type 2 diabetes. However, two potential pitfalls are that these drugs can be prescribed off label for other uses, and also the use of insulin is not specific for type 2 diabetes, as insulin may also be used in the treatment of other forms of diabetes (most commonly type 1 diabetes).

> *Fasting plasma glucose ≥ 7 mmol/L (≥ 126 mg/dL) or 2-hr plasma glucose ≥ 11.1 mmol/L (200 mg/dL) after a 75-g oral glucose load.*

Again, these are the cutoffs recommended by ADA, but only single measurements seem to be made. **As stated above at least 2 abnormal results** would be required in the absence of unequivocal hyperglycemia.

> *Meeting at least one of the four criteria: fasting plasma glucose ≥ 7 mmol/L, random plasma glucose ≥ 11.1 mmol/L, use of anti-diabetes medication, and/or following dietary guidelines for type 2 diabetes.*

As previously discussed, two measurements of FPG are generally required to confirm the diagnosis of diabetes and random plasma glucose >11.1 mmol/L alone would not meet diagnostic criteria for type 2 diabetes unless accompanied by clinical signs of hyperglycemia or hyperglycemic crisis. Again, use of an anti-diabetes medication that is indicated only for the treatment of type 2 diabetes may suggest a diagnosis of type 2 diabetes, but this would not be definitive. We disagree with using dietary guidelines as the basis for determining a diagnosis of type 2 diabetes, as these diets may be recommended to patients who are at risk for (but have not yet developed) type 2 diabetes or may be followed for general health reasons (e.g., weight loss).

Validated Surrogate Endpoints for Type 2 Diabetes

3. *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: According to 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. Elevated blood sugar concentrations and insulin resistance are listed as examples of surrogate endpoints for risk of type 2 diabetes in that guidance document. Note that 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 $\geq$ 126 mg/dL or 7

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

mmol/L, elevated 2-hour glucose $\geq$ 200 mg/dL or 11.1 mmol/L following 75-g OGTT, or elevated hemoglobin A1c $\geq$ 6.5%) and not clinical outcomes such as development of diabetic complications.

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 therefore may be considered to have "prediabetes." The ADA has proposed the following three laboratory criteria to define prediabetes (1), indicated in **Table 2**:

Table 2: Criteria to define prediabetes (adapted from ADA Standards of Medical Care, 2020)

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 risk of diabetes is continuous, extending below the lower limit of the range and becoming disproportionately greater at the higher end of the range.

Insulin resistance has long been associated with increased risk of developing type 2 diabetes. However, 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 (1). 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 (4). Many individuals with obesity and insulin resistance may never develop type 2 diabetes if they do not develop β cell dysfunction (5). Once present, β cell dysfunction results in impaired glucose homeostasis which can be measured directly by blood glucose laboratory criteria.

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 (2). Risk of diabetes appears to be greatest in individuals with combined IFG and IGT when

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

compared to those with isolated IFG or IGT (3). 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 (6).

For the purposes of health claims, we recommend using the prediabetic criteria (as detailed in **Table 2**) as surrogate endpoints for risk of type 2 diabetes. Evidence of insulin resistance when combined with prediabetic criteria would strengthen risk for type 2 diabetes. Insulin resistance alone (without evidence of prediabetes) is not as significant a risk for type 2 diabetes.

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 resistance 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, Avignon's SiM, have been shown to correlate strongly with hyperinsulinemic euglycemic clamp results (7) and in our view would be acceptable measures of insulin sensitivity/resistance for health claim evaluations.

<u>In summary, we recommend the following surrogate endpoints for risk of type 2 diabetes:</u>

1) 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)
2) *Insulin resistance (*to be used only in combination with prediabetic criteria*). 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 (7)

4. *Is there any other surrogate endpoint for type 2 diabetes that is not listed in the 2012 CDER/DMEP consult (e.g., HbA1c)?*

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

DDLO Response: See response to Q3.

5. *If insulin resistance is still considered a valid surrogate endpoint for type 2 diabetes (as listed above in the 2012 CDER/DMEP consult), which methodologies are valid/acceptable for estimating insulin resistance?*

DDLO Response: See response to Q3.

C. Additional Questions from CFSAN

Following a teleconference between DDLO and CFSAN on 5/19/2020, CFSAN submitted the following additional consult questions on 5/29/2020:

6. Are there any approved drugs for reducing the risk of type 2 diabetes?

DDLO Response: No pharmacologic therapies are approved by the FDA for prevention of type 2 diabetes. In research studies of patients with prediabetes, metformin, α-glucosidase inhibitors, glucagon-like peptide 1 receptor agonists, thiazolidinediones, and several weight-loss drugs (e.g. tetrahydrolipstatin, topiramate/phentermine) have been shown to decrease the incidence of diabetes to various degrees (8), however there are concerns regarding the risk-benefit balance for many of these pharmacologic agents. Due to metformin's overall strong evidence base (9) and long-term safety data, the ADA has recommended that metformin be considered for prevention of type 2 diabetes in those with prediabetes, especially for those with BMI > 35 kg/m2, those aged <60 years, and women with prior gestational diabetes mellitus (10). It is important to note that the ADA has not recommended any pharmacologic treatment for patients with insulin resistance who do not have prediabetes.

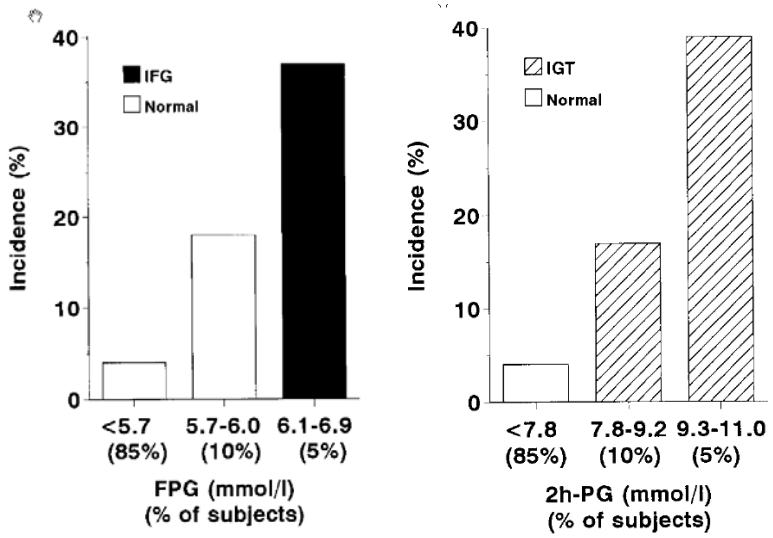
7a. Is it appropriate to include studies involving healthy subjects (i.e. normal values of plasma glucose or HbA1c) and studies involving subjects with blood glucose values within the prediabetic range when evaluating the effect of a substance on reduced risk of type 2 diabetes? Please explain.

DDLO Response: As stated in our response to Question 3, there is strong evidence that abnormally elevated blood glucose in the prediabetic range (as represented by the criteria of IFG, IGT and prediabetic HbA1c) confers a high risk for future development of type 2 diabetes (2, 3, 6). The cutoffs are widely used in clinical practice to identify high-risk patients and to institute preventative measures (including

lifestyle changes and the pharmacologic interventions discussed in our response to Question 6b).

However, the risk of type 2 diabetes appears to be continuous, extending below the lower limit of the stated ranges and becoming disproportionately greater at the higher end of the range (1). For example, the 5-year incidence of diabetes in Pima Indians progressively increased according to baseline fasting plasma glucose [Figure 1, taken from Gabir et. al, 2000 (11)]

Figure 1: Cumulative incidence of diabetes in normal fasting and 2-hour plasma glucose during OGTT, impaired fasting glucose and impaired glucose tolerance using 1999 WHO criteria[6] (11)



Similar data is available for HbA1c. The 5-year risk of developing type 2 diabetes in individuals with HbA1c between 6% and 6.5% is 25 to 50%, with a relative risk 20-fold higher compared to individuals a normal HbA1c of 5% (6).

Overall, the magnitude of risk for type 2 diabetes declines substantially with normal values of plasma glucose or HbA1c. Given that the risk is continuous along the blood glucose spectrum, studies in healthy subjects could be informative. However, given that the baseline risk of type 2 diabetes is much lower in a population with normal glucose metabolism, the effect size (i.e., risk reduction) is likely to be small.

[6] The 1999 WHO criteria defined impaired fasting glucose by FPG $\geq$6.1 to < 7.0 mmol/L.

7b. When evaluating the effect of a substance on type 2 diabetes, is it appropriate to include studies involving healthy subjects (i.e., normal values of plasma glucose or HbA1c) when the endpoint is incidence of type 2 diabetes?

DDLO Response: Yes.

D. References

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