Foods to decrease the renal threshold of glucose in type 2 diabetes: Making the case to research and adopt a food urinary glucose index (FUGI).

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Editorial

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More die in the United States of too much food than of too little.

John Kenneth Galbraith

An insulin-independent glucose excretory model for treating type 2 diabetes (T2D) is gaining traction in recent years, with mainstream adoption of sodium-glucose cotransporter 2 (SGLT2) inhibitors that reduce the reabsorption of glucose from the urine in patients with a normal glomerular filtration rate (GFR) and thus promote glycosuria.

Methodology exists to classify foods according to how much postprandial insulin they release, using white bread, a maximum insulinotropic food, as a reference. The food insulin index (FII) is one such metric for individual foods whose correlation with postprandial measured insulin demand is greater than either the calculated glycemic load or the carbohydrate content. The FII is calculated by measuring the insulin response (area under the curve) upon administration of isoenergetic single foods. The FII is expressed as the area under the curve relative to that for white bread.

The renal threshold for glucose (RTG) is defined as the minimum concentration of glucose in the blood at which glucose begins to appear and increase in the urine. There is a general agreement that the hyperglycemia caused by T2D occurs at least in part because the RTG is increased. Analogous to the existing FII for different foods and food-groups, there does not yet exist a food urinary glucose index (FUGI), which would measure the food-induced change in urine glucose (UG) levels relative to (say) an SGLT2 inhibitor in T2D patients and then assign each individual food, a FUGI value using the SGLT2 inhibitor value as a reference. The FUGI would be complementary to – but not necessarily overlap; and may, in some cases, even be effect divergent to – the FII, because foods that cause the RTG to decrease may act via different signaling pathways than those (foods) that stimulate insulin secretion in response to increased blood glucose levels. An example is the dihydrochalcone glucoside, phlorizin, which occurs naturally in apples. Phlorizin is both an SGLT1 and an SGLT2 inhibitor and was the starting molecular template for synthetic SGLT2 inhibitors. Apple juice has a moderately high FII due to the presence of carbohydrates but is likely to have a high FUGI as well due to the presence of phlorizin,

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hence it may not necessarily be as inimical to a T2D diet as it is thought to be because its capability to decrease RTG may significantly outweigh its propensity for increased insulin demand. On the other hand, foods such as walnuts, peanut butter, tuna, and eggs have a greater ratio of fat to carbohydrate and moderately low FII values. However, a high-fat content has been found to decrease adiponectin levels thereby leaving SGLT2 function unaffected. Hence, these foods with a moderately low FII; which T2D patients tend to consume in larger proportion precisely because of this reason, may not be as beneficial because of their low FUGI. The ideal foods are obviously those that have a moderately low FII and a high FUGI, such as tomatoes, eggplants, spinach, brown rice, turmeric, and a whole host of plant-based foods and food products that collectively reaffirm the health benefits of the Mediterranean diet. The greater the ratio of the FUGI to the FII for a particular food or food ingredient, the better this paradigm is served.

The literature indicates that IC^{50} values of the active ingredients at their concentrations present in most relevant foods are comparable to those of SGLT2 inhibitors. This suggests that normal dietary intake of such foods may be sufficient to cause detectable changes in the UG. It may be that, in specific instances, measurable decreases in the RTG may require acute ingestion of prohibitively large quantities of a particular food(s) or food ingredient(s). However, statistical significance in acute studies is not necessarily correlated to clinical outcomes in chronic studies because mildly perturbed effectors and/or signaling pathways over a longer time interval may turn out to be equipotent to significantly greater perturbations on an acute level. It is, therefore, possible that long term statistically insignificant increases in UG may cause clinical outcomes that can only be detected or predicted by acute large magnitude exposure. Therefore, *in vitro* FUGI values measured by exposing SGLT2 expressing cells to excessively large isoenergetic concentrations of foods or food ingredients may not necessarily invalidate its credibility as an accurate indicator of RTG modulation when those foods are ingested at dietary relevant concentrations over long time intervals. This is especially relevant because the duration of T2D has been shown to be independently associated with a high RTG. In these specific instances for these foods, the FUGI – even though seemingly unrepresentative of normal ingested quantities – may nevertheless provide an incontrovertible indicator of food effectiveness in reducing RTG over the long term.

FUGI values can be assigned, not only to foods or food ingredients, but also to signaling pathway relevant natural remedies or supplements. Such a designation can enable T2D patients to consume moderately high FII diets along with high FUGI natural remedies or supplements. It must be emphasized here that the objective of creating the FUGI is not to allow consumption of T2D unfriendly high-carbohydrate diets or to indulge in outright gluttony – although this temptation of subversion exists - but to act synergistically with low FII foods. As with the adoption of any new biological index, dietary studies that compare the incidence of cancer development using the FII alone, versus using a combination of the FII and FUGI will determine the efficacy of the FUGI and the validity of the glucose excretory model for treating T2D.

The limit of detection (LOD), precision and accuracy of non-enzymatic UG detection methods have improved to the extent that statistical significance can be obtained with UG differences as low as 30 nM. This contrasts with the LOD of the order of 600 nM obtained by the classical enzymatic glucose-oxidase method. The literature suggests that the average difference between RTG of normal and T2D patients is of the order of 1300 nM. Therefore, even if a muted UG response is the norm for highly variable blood glucose concentrations, the improved methods should clearly be able to discriminate with an accuracy of 2% or more between the magnitude of postprandial increase in glycosuria (or a decrease in RTG) caused by a particular food. It may be that certain foods actually increase RTG; in which case, they should be specifically avoided even if they elicit a postprandial insulin demand comparable to their isoenergetic food-group counterparts.

As accepted clinical practice for the management of

T2D patients transitions from an insulin secretory to a glucose excretory model, the biological indicators to measure the effectiveness of drugs or foods must be expanded to include the glucose concentration in the urine and the renal threshold of glucose. Since the diet constitutes an important facet of combating metabolic disorder, an index to measure the relative efficacy of various foods to increase UG or decrease RTG must be devised and adopted. A proposed index, FUGI, for various food-groups, foods, food ingredients, natural remedies or supplements may be iteratively combined with the FII such that the resultant diet becomes maximally glycosuric (high FUGI) and minimally insulinotropic (low FII).