Merit of Incremental Area under the Curve (iAUC) in Nutrition is Varied in Pharmacological Assay- A Review

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Abstract

The area under the curve (AUC) is developed to quantify the total rise in blood glucose during an oral glucose tolerance test (OGTT) in clinics. Similarly AUC is also used in the assay of new agent(s) development for diabetes in animals. In clinics variations in fasting plasma glucose of each case have been suggested to rule out by subtracting the baseline showing at the 0 min during OGTT. Then the incremental area under the curve (iAUC) value is developed and it is also applied in the calculation of the glycemic index (GI) of foods in nutrition. Additionally iAUC has ever been used to rule out the variations in fasting plasma glucose between genetic animals and the wild-type littermates. However it is limited in the cases that received acute treatment only. Taken together we suggest that modification of the baseline values shall be careful. The basal glucose level and/or fasting plasma glucose must include in the calculation of AUC during OGTT in animals received a chronic treatment which is widely applied in the pharmacological assay. Therefore the treated method is mainly associated with the application of iAUC or not.

Keywords: Area under the curve (AUC); Oral glucose tolerance test (OGTT); Incremental area under the curve (iAUC); Glycemic Index (GI); Diabetes

Abbreviations: T2DM: Type-2 Diabetes; OGTT: Oral Glucose Tolerance Test; IGT: Impaired Glucose Tolerance; AUC: Area Under The Curve; iAUC: The Incremental Area Under The Curve; tAUC; The Total Area Under The Curve; pAUC: Positive Incremental Area Under The Curve; GL: Glycemic Load; GI: Glycemic Index; ZDF: Zucker Diabetic Fatty

Background

Oral glucose tolerance test (OGTT) is one of the popularly used tools in the clinic because it is widely indicated to diagnose for the impaired glucose tolerance (IGT) [1]. As described in our previous report [2], the shape of glucose curve during OGTT is mainly employed to reveal the risk

of developing IGT and the patterns of insulin concentration are also applied to predict the development of T2DM. Therefore the diabetic experts can diagnose the progress of diabetic disorders using OGTT.

Because OGTT did not show the total rise in blood glucose level [3], the area under the curve (AUC) is then developed to quantify the total rise in blood glucose during an OGTT. Usually, AUC of OGTT is calculated using the trapezoidal rule [4]. Therefore the assessment of total blood glucose response vs time during OGTT is developed to apply in clinics. However, the baseline of fasting plasma glucose in each case is not the same. Alternatively the incremental area under the curve (iAUC) has been developed [5,6]. However the subtracting baseline value has been criticized to be problematic [7] due to the presence of negative values. Then IGT: impaired glucose tolerance has further been developed and only the values above the baseline value were considered to apply in the studies [5,6]. Totally it included the total area under the curve (tAUC) incremental area under the curve (iAUC) and positive incremental area under the curve (pAUC) in clinical practice. The cut-off baseline values (iAUC) have been challenged not only by the mathematical view [7] but also by the clinical report [8]. In recent the correlation studies of AUC and glucose levels during OGTT demonstrated that tAUC showed the best correlation with the 2-hour glucose level of OGTT and the total glucose response is better represented by the tAUC rather than iAUC or pAUC in clinics [9].

Scenario 1

Generally iAUC has been applied to calculate the Glycemic Index (GI) in nutrition the GI of a food is defined by the incremental area under the blood glucose curve (iAUC) after the ingestion of 50 grams of carbohydrates in a test food showing as a percentage of the iAUC of an equal amount of a reference food (glucose) [10]. Therefore GI = (iAUC for the test food containing 50 g of available carbohydrate/iAUC of a standard food with an equal carbohydrate portion) × 100 %. The GI of each tested food was taken as the mean value for the whole group of subjects. Foods that are classified as low GI provide a better response to postprandial glucose causing a slight increase in circulating levels of insulin and gastrointestinal hormones. Therefore satiety is increased and voluntary food intake is reduced [11]. The GI concept has clinical benefits for preventing and/or treating some chronic diseases such as diabetes, cardiovascular disease, and some cancers or obesity [12]. Additionally the GI has further developed to glycemic load (GL) that is generally calculated according to the formula: GL = (GI of test food × amount of carbohydrate in a serving of test food (g))/100 [13]. Therefore GI and GL are widely used in nutrition

particularly several international GI tables have been established [14].

Pharmacologically the test substance is treated by two ways one is the acute treatment and another is the repeated chronic treatment. In acute treatment a test substance is treated prior to the oral intake of glucose at a short-time (together or 30 - 60 min) in general. Therefore it is similar to the calculation of GI because the fasting plasma glucose is not markedly modified and iAUC from OGTT is suitable to apply. For example mutant mice and the wild-type littermates showed various fasting blood glucose level [15]. Correction of the data in basal glucose level has ever been suggested [16] but no report followed. In one report iAUC has been applied to study the changes in Zucker diabetic fatty (ZDF) rats [17]. Functionally ZDF rats suffer diabetic disorders after 12 weeks old. Therefore iAUC was used to compensate for the variations in basal glucose level between 8-week-old group (normal animals) and 13-week-old group (diabetic animals). The tested two agents canagliflozin and sitagliptin were simultaneously administered with glucose solution (2g/kg) to the overnight fasted ZDF rats. However from the results of OGTT, iAUC values for fasting glucose level (control) between normal group and the diabetic group were still markedly different. It means that iAUC in OGTT failed to compensate for the variations in fasting plasma glucose between diabetes and normal animals. Therefore in addition to the bias of age it failed to rule out the variations in fasting plasma glucose between genetic animals and the wild-type littermates after an acute treatment.

Scenario 2

Otherwise iAUC is not suitable to apply in another treated method that is widely used in the pharmacological assay. As described in our previous report [2], no paper ignored or deleted the values of fasting plasma glucose or basal glucose level in the calculation of AUC using OGTT to screen the efficacy of agent(s) in recent 10 years (2007–2017). Another method is a daily repeated treatment chronic method including more complicated parameters. Herbal extract the new agent or nutrient is applied to treat the diabetic animals once or several times daily at the desired dose. Generally each test substance is repeatedly treated for one week or more. Then the treated diabetic animals are employed to receive OGTT. Mostly the fasting plasma glucose is markedly reduced in these animals showing the influence of test substance [18]. The reduction in fasting plasma glucose has been mentioned to link with the changes in hepatic glucose homeostasis [19]. Overall changes in fasting plasma glucose belong to the cumulative effects of test substance after a repeated treatment in animals. Therefore the derived fasting

plasma glucose level shall be included in the calculation of AUC. Depending on this truth, iAUC is not suitable to apply in the animals receiving chronic treatment. However the real mechanism(s) for it remained unknown. Therefore scientific evidence(s) for the role of fasting blood glucose or basal glucose level showing at the 0 min during OGTT is extremely required.

Conclusion

The area under the curve (AUC) is used to quantify the total rise in blood glucose during an oral glucose tolerance test (OGTT) in clinics. Variations in fasting plasma glucose levels between individuals have been ruled out by subtracting the baseline showing at the 0 min during OGTT to develop the incremental AUC (iAUC). The iAUC value is also applied in the calculation of the glycemic index (GI) in nutrition. Otherwise AUC is employed in the assay of new agent(s) development for diabetes in animals. The iAUC has ever been used to rule out the variations in fasting plasma glucose between genetic animals and the wild-type littermates. But it seems not useful and iAUC is limited in the cases received acute treatment only. Taken together we suggest that modification of the baseline values shall be careful. The basal glucose level and/or fasting plasma glucose must include in the calculation of AUC during OGTT in animals received a chronic treatment which is widely applied in the pharmacological assay. Therefore the treated method is linked to the application of iAUC or not.

Acknowledgement

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