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Review article

Glycative stress and anti-aging: 13. Regulation of Glycative stress. 1. Postprandial blood glucose regulation

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Abstract

Lifestyle and dietary habits aiming at the inhibition of glycative stress are called anti-glycation. The inhibition of postprandial hyperglycemia is one of the specific countermeasures for anti-glycation. Although there are several hormones which raise lowered blood glucose level, insulin secreted from β-cells of the pancreas is the only hormone which can lower blood glucose levels. β-cells and GLUT2 (glucose transporter 2) of the pancreas detect rises in blood glucose level caused by eating and work to take glucose into cells. The insulin secreted fromβ-cells facilitates the uptake of glucose to skeletal muscles and fat cells via glucose transport 4 (GLUT4), and at the same time, it promotes glycometabolism by working on glucolysis. Exercise has acute and chronic effects on the level of blood glucose. The acute effects consume energy and lower blood glucose levels in association with skeletal muscle contraction. The chronic effects increase insulin sensitivity. Exercise inhibits the rise of blood glucose levels and improves insulin resistance. Meanwhile, when blood glucose levels fall, α-cells of the pancreas secrete glucagon. Glucagon breaks down the glycogen accumulated in the liver and raises blood glucose levels.

Dietary ingestion stimulus makes the small intestine secrete glucose-dependent insulinotropic polypeptides (gastric inhibitory polypeptide (GIP) and glucagon-like peptide-1 (GLP-1)). These digestive tract hormones are called incretins. Incretins are hormones that enhance the secretion of insulin. Because GLP-1 is rapidly broken down and deactivated by dipeptidyl peptidase-4 (DPP-4), its blood half-life is as short as one to two minutes. Therefore, recently, diabetes drugs taking measures which focus on DPP-4 have been gathering attention.

The α-glucosidase in the saliva and pancreas juice breakdown the polysaccharides included in food into monosaccharides. The α-glucosidase inhibitors inhibit the actions of enzymes which break down the carbohydrates ingested by meals into monosaccharides. Therefore, the intake of α-glucosidase before meals is useful for the inhibition of postprandial hyperglycemia.

Glycemic index (GI) of foods is one of the useful information for dietary guidance for diabetes and metabolic syndrome. Blood-glucose levels increase less sharply after the intake of low GI food. GI levels differ depending on the amount of carbohydrates, diet fiber, lipids, and protein included in food and its degrees of purity and processing. The rise of postprandial blood-glucose levels can be inhibited also by adding water-soluble dietary fiber to meals. Intake of vegetable salads before steamed rice can lower postprandial blood glucose levels. The intake of carbohydrates and side dishes at the same time produces a similar effect. Furthermore, rises in postprandial blood glucose levels can be inhibited by decreasing the amount of carbohydrates in meals; however, carbohydrates are one of the important nutrients, so excessive restriction of carbohydrates may possibly increase the risk of death.

At the time when postprandial blood glucose levels rise, blood aldehyde levels also rise. This phenomenon is called aldehyde spark. It is reported that methylglyoxal, one of the aldehydes in blood, induces inflammation in vascular endothelium. Aldehydes are intermediate glycative reaction products, and the rise of its concentration in blood possibly promotes the generation of AGEs and increases glycative stress. For anti-glycation, the inhibition of postprandial aldehyde is also important in addition to postprandial hyperglycemia.

***KEY WORDS*:** postprandial hyperglycemia, incretin, α-glucosidase inhibitor, glycemic index

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1. Introduction – Countermeasures for Glycative Stress

Living habits and dietary habits aiming at the inhibition of glycative stress are called anti-glycation [1]. The fundamentals of anti-glycation are to live daily life having a consciousness of lowering glycative stress. The living habits that we should be conscious of are the maintenance of muscle mass, adequate exercise, appropriate dietary habits, and alleviation of mental and physical stresses. Specific measures are inhibition of postprandial hyperglycemia, inhibition of glycation reaction, and breakdown and excretion of generated AGEs. In this paper, the relationship between diet and blood glucose level and the method to inhibit the rise of postprandial blood glucose level after meals are explained.

2. Hormone Regulatory Function between Blood Glucose and Glycometabolism

The cells *in vivo* are transforming the glucose taken from blood into adenosine triphosphate (ATP), an energy source, and using it. Because the brain greatly depends on glucose for ATP synthesis, it is strongly influenced by the lowering of blood glucose levels. The hormones which raise the lowered blood glucose level *in vivo* are glucagon, growth hormones, epinephrine (adrenaline), and corticosteroid. These hormones take glucose into skeletal muscles and fat cells via glucose transporter and control glycometabolism in cells. Meanwhile, the only hormone which lowers blood glucose level is insulin (*Fig. 1*) [2]. It is considered that this imbalance has been equipped for humans to survive against hunger.

The fasting blood glucose levels of healthy persons are 70-90 mg/dL. However, the postprandial blood glucose level rises above140 mg/dL, even though it is dependent upon the volume and quality of meals. The condition where postprandial blood glucose level rises above 140 mg/dL is called glucose spike [3, 4]. The rise of blood glucose level is detected by the hypothalamus of the brain, and its signal is transported to β-cells of the pancreas via parasympathetic nerves and insulin is secreted. There is glucose transporter 2 (GLUT2) in β-cells and it takes glucose into cells, depending upon blood glucose levels (glucose concentration in blood). β-cells detect the rise in blood glucose level by responding to this signal and secrete insulin. Insulin promotes the uptake of glucose via glucose transport 4 (GLUT4) in skeletal muscles and fat cells, and at the same time, enhances glycometabolism, by acting on glucolysis. As a result, the blood glucose levels raised by taking meal decline about up to 100 mg/dL.

Meanwhile, when hypothalamus detected the fall of blood glucose level, α-cells of the pancreas are stimulated by the sympathetic nerve and glucagon is secreted. In the liver, glucagon is activated by phosphorylating glycogen phosphorylase, and the glycogen accumulated in the liver is broken down and becomes glucose, which is then secreted into the blood. As a result, blood glucose levels rise.

The fluctuations of blood glucose levels after meals are controlled by the action mechanism of hormones so that the level between meals becomes about 100 mg/dL.

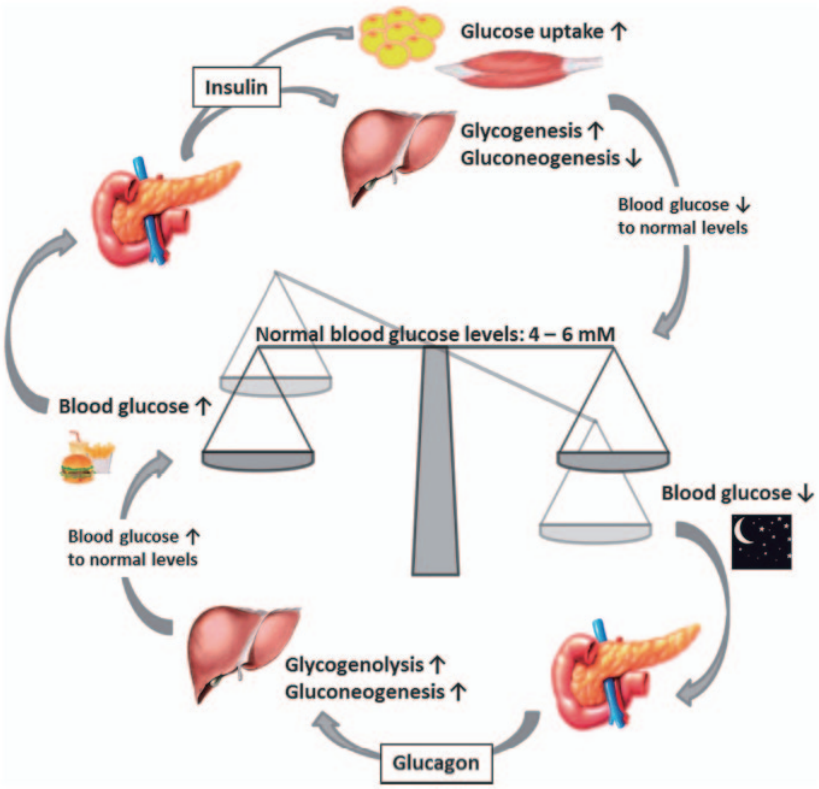

Fig. 1. **Maintenance of blood glucose levels by glucagon and insulin.**

When blood glucose levels are low, the pancreas secretes glucagon, which increases endogenous blood glucose levels through glycogenolysis. After a meal, when exogenous blood glucose levels are high, insulin is released to trigger glucose uptake into insulin-dependent muscle and adipose tissues as well as to promote glycogenesis. The figure is adapted from Reference 1.

3. Carbohydrate Digestion/Absorption and Incretins

Polysacchaides (carbohydrates) included in foods are broken down into disaccharides by saliva and α-amylase in pancreatic juice. After that, the disaccharides that reached small intestine are broken down by α-glucosidase existing on brush border in mucosal epithelial cells having microvillus into monosaccharides and absorbed in body. α-glucosidase includes maltase breaking down maltose and converting it to two molecules of glucose, sucrase breaking down sucrose into fructose and glucose and isomaltase breaking down isomaltose and convert it to two molecules of glucose.

Two kinds of hormones of glucose-dependent insulin secretion stimulating polypeptide (gastric inhibitory polypeptide (GIP)) and glucagon-like peptide-1 (GLP-1) are secreted from small intestine by the dietary ingestion stimulus *in vivo,* and these digestive tract hormones are called incretins. The incretins increased by continued meal intake activate β-cells in the pancreas and facilitate insulin secretion. By these actions, rises in postprandial blood glucose levels are inhibited. Incretins are a group of digestive tract factors facilitating the additional secretion of insulin, and the insulin secretion promotion by incretins contributes to the homeostasis of blood glucose levels.

K cells secreting GIP locally exist mainly in duodenum, the upper part of the small intestine, with its center on jejunum. Meanwhile, L cells secreting GLP-1 are considered to exist in the lower small intestine (***Fig. 2***)[5]. K cells and L cells detect the nutrients that reached the intestinal tract, and each of them secretes GIP and GLP-1 to basolateral plasma membrane side, respectively. The rise of GLP-1 concentration in the blood is observed immediately after meals and continues for one to two hours. GIP also rises immediately after meals and its level in blood continues to rise for more than several hours. Nutrients facilitating the secretion of incretins include carbohydrates. The secretion of incretins by carbohydrates is considered to be caused by the carbohydrates absorbed by sodium-glucose cotransporter 1 (SGLT1) which cause depolarization of cell membranes, and as a result, the secretions of GLP-1 and GIP are facilitated. Besides carbohydrates, protein, peptide and fat are considered to facilitate the secretion of incretin.

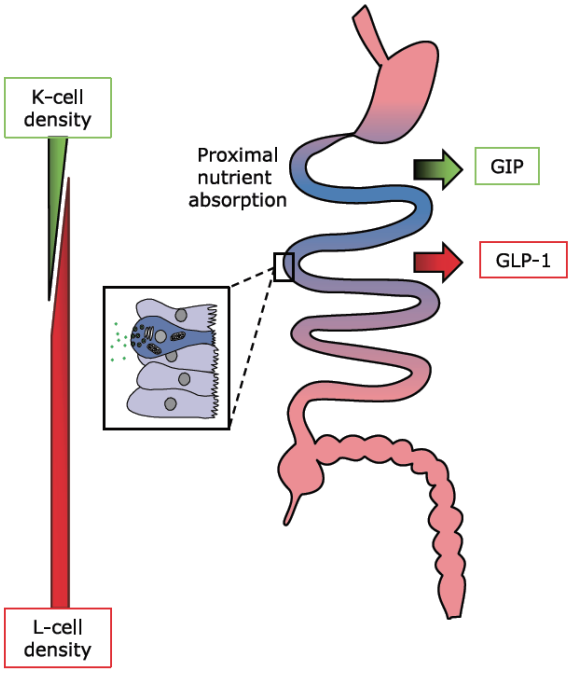

Fig. 2. **Incretin hormone secretion from K and L cells.**

Glucose dependent insulinotropic polypeptide (GIP) is secreted from K cells, which are predominantly found in the duodenum, whereas glucagon-like peptide-1 (GLP-1) is secreted from L cells, which increase in numbers in the distal intestine. The figure is adapted from Reference 5.

4. Exercise and Glycometabolism

The glucose in blood is taken into cells via GLUT4. Blood glucose levels rise by taking in meals and the amount of insulin commensurate with it is secreted from the pancreas. After that, insulin connects with insulin receptors existing on the surface of cells and the receptors issue the signal that they will take glucose into cells. With this signal transduction, GLUT4 within cells moves to the surface of cells and takes glucose in the blood into cells. If the level of insulin falls due to aging and diabetes, the signal transduction ability via insulin receptors decrease. Therefore, GLUT4 become unable to move to the surface of cells and its action of taking glucose in blood into cells decreases. This condition is called insulin resistance. The amount of GLUT4 moving to the surface of cells is increased by muscle contraction stimulus through exercise. Furthermore, the amount of GLUT4 moving to the surface of cells is increased by the continuance of exercise. The homeostasis of blood glucose levels can be maintained by these actions[6].

The effects of exercise are divided into acute effects and chronic effects. An acute effect is energy consumption. AMP kinase detects the rise of AMP/ATP accompanied by muscle contraction of skeletal muscles which increases the uptake of glucose, and as a result, blood glucose levels fall[7]. Because the promotion of glucose transport by exercise is a mechanism different from insulin response, even persons with insulin resistance can lower blood glucose levels through exercise. As blood glucose level is highest for 30 minutes to one hour after meals, postprandial hyperglycemia can be effectively inhibited by aerobic exercise during this time[8].

The increase of insulin sensitivity is a chronic effect. This mechanism includes GLUT4, increase of protein volume, increase of blood flow to motor muscles, decrease of body fat and increase of insulin signaling protein[9]. Therefore, exercise can inhibit the rise of blood glucose levels and is a factor for the improvement of insulin resistance. The recommended kinds of exercises are muscle training, stretching and aerobic exercises such as walking, jogging and swimming.

5. Meal and Enzyme Inhibitor

α-Glucosidase inhibitor (GI) inhibits the absorption of glucose from the upper part of the small intestine by inhibiting the actions of enzymes breaking down glucose ingested as meals to monosaccharides, and as a result, inhibits the rise of postprandial blood glucose levels. In Japan, mainly the three drugs of acarbose (drug name: Glucobay), voglibose (drug name: Basen) and miglitol (drug name: Seibule) are used for

the treatment of diabetes. Acarbose and voglibose are rarely absorbed via the intestinal tract. However, miglitol is partially absorbed via the small intestine and excreted in urine from kidneys in its original form. Acarbose inhibits not only the action of α-glucosidase, but also that of α-amylase.

The inhibitory action of α-glucosidase exists also in foods. Guava leaf polyphenol (maltase, sucrase and amylase inhibiting action), wheat albumin (amylase inhibiting action), L-arabinose (sucrase inhibiting action) and fermented soybean-deriver *touchi* extract (α-glucosidase inhibiting action) are food materials expected to have the effect of inhibiting the rise of postprandial blood glucose levels.

Incretins are the hormones secreted from secretion cells in the digestive tract after meals. They facilitate the secretion of insulin. However, GLP-1 is rapidly broken down and inactivated by dipeptidyl peptidase-4 (DPP-4) exiting in the whole body, so their half-life in blood is as short as 1-2 minutes. Therefore, recently, diabetes drug taking measures focused on DPP-4 is gaining more attention. There are GLP-1 receptor drugs with resistance to DPP-4 such as liraglutide (drug name: Victoza) and exenatide (drug name: Byetta and Bydureon). There are various DPP-4 inhibitors such as sitagliptin (drug name: Januvia and Glactiv), vildagliptin (drug name: Equa), alogliptin (drug name: Nesina), linagliptin (drug name: Trazenta), teneligliptin (drug name: Tenelia), anagliptin (drug name: Suiny), sxagliptin (drug name: Onglyza), trelagliptin (drug name; Zafatek) and omarigliptin (drug name: Marizev).

6. Meals That Do Not Have a Tendency to Raise Blood Glucose Levels

Jenkins *et al*. reported in 1981 that there are differences in the degrees and speeds in the rises of blood glucose levels, even if the amounts of carbohydrates in meals are the same [10]. After that, they proposed the method to calculate glycemic index (GI) of foods by relatively comparing the area under the curve (AUC) of blood glucose after meals when 50 g of 62 kinds of foods was eaten and when the same amount of glucose was eaten, targeting healthy subjects without diabetes. Since then, the GI of foods has become useful information for the dietary guidance for diabetes and metabolic syndrome. Whereas GI shows the effect of the "quality" of carbohydrate on blood glucose levels when a certain amount of carbohydrates were eaten, its effect on blood glucose levels is different also based on the quantity of carbohydrates eaten. Salmeron *et al*. devised glycemic load (GL) as an index, by taking into account the "quality" and "quantity" of carbohydrate ingested by a meal [11]. The quantities of carbohydrates of foods are shown by %, and GL is obtained by multiplying GI of foods by the rate.

Generally, foods with a GI value higher than 70 are regarded as high-GI foods, those with a GI value of 56-69 are regarded as medium-GI foods, and those with a GI value of 55 or less are regarded as low-GI foods. When low-GI food is digested, AUC is smaller than when high-GI food is ingested, so that a mild rise in blood glucose levels can be expected. GI values are different depending on the amount of carbohydrates, diet fiber, lipids and protein included in food, as well as degrees of purity and processing method. Originally, GI value is an index of the degree of the rise of blood glucose levels when 50 g of carbohydrates was ingested, which is shown by a relative value presuming the same amount of glucose in standard food is 100. However, in the information shown for GI values, there are different kinds of foods (steamed rice and bread) and those with different carbohydrate volumes. In Japan, the Japanese Association for the Study of Glycemic Index is recommending the verification of a unified protocol for the study of glycemic index based upon 147 g of packed rice (equivalent to 50 g carbohydrate) as a standard food [12].

It is possible to moderate the rise of postprandial blood glucose levels by adding dietary fiber to meals. When indigestible dextrin, a kind of water soluble dietary fiber, is digested together with carbohydrates and monosaccharides, it swells up with water, delays the speed of sending food from stomach to intestine, becomes sticky and gelatinous in the small intestine and inhibits the diffusion of food, and as a result, breakdown enzymes have difficulty contacting the food which delays the digestion/absorption of carbohydrates. Therefore, foods with the addition of indigestible dextrin inhibit the rise of postprandial blood glucose levels. The effect of indigestible dextrin is expected to inhibit the rise of postprandial blood glucose levels and it is used as Food for Specified Health Uses in Japan [13].

Meanwhile, the rise of postprandial blood glucose levels differs depending on food intake sequence. When eating 200 g of steamed rice and 60 g vegetable salad, eating vegetable salad before steamed rice makes the rise of postprandial blood glucose level lower, and it also moderates insulin secretion [14]. Triggered by this report, a health management method based upon food intake sequence is gathering attention as a countermeasure for the rise of postprandial blood glucose levels [15]. For the inhibition of the rise of postprandial blood glucose levels, there are useful dieting methods such as eating grapefruit [16] or plain yogurt (***Fig. 3***) [17] before carbohydrates, adding dietary fiber to noodles [18], not eating carbohydrates such as noodle and steamed rice alone, but together with side dishes such as egg, vegetable salad, mapo eggplant [19] and gyudon (beef bowl) topping [20].

Furthermore, for the purpose of inhibiting the rise of postprandial blood glucose level, there is a method to decrease the amount of carbohydrates in meals. This is called carbohydrate restriction. However, carbohydrates are one of the important nutrients. There are research results that state an excessive restriction of carbohydrate may possibly increase the risk of death [21].

7. Postprandial Hyperglycemia and Aldehydes in Blood

It is reported that at a time of postprandial glucose spike, the rises of aldehydes in blood such as 3-deoxyglucosone, glyoxal and methylglyoxal occur (***Fig. 4***) [22, 23]. This phenomenon is called an aldehyde spark [24]. It has been shown that methylglyoxal induces inflammation in vascular endothelium [25]. It is also reported that glyoxal and methylglyoxal in blood induce the activation of the mitogen-activated protein kinase (extracellular signal-regulated kinase, ERK, c-Jun N-terminal kinase, JNK) in human umbilical vein endothelial cells [26, 27]. From the above, it is possible that a rise of the postprandial blood glucose level is accompanied by an aldehyde spark, and as a result, blood aldehyde gives rise to cell damage in vascular endothelium.

Aldehyde is a glycation intermediate, and it is possible that the rise of its concentration in blood promotes the generation of AGEs, and possibly enhances glycative stress. Therefore, for the inhibition of glycative stress, it is important to inhibit postprandial aldehyde as well as postprandial hyperglycemia.

Conflict of Interest Statement

The authors claim no conflict of interest in this study.

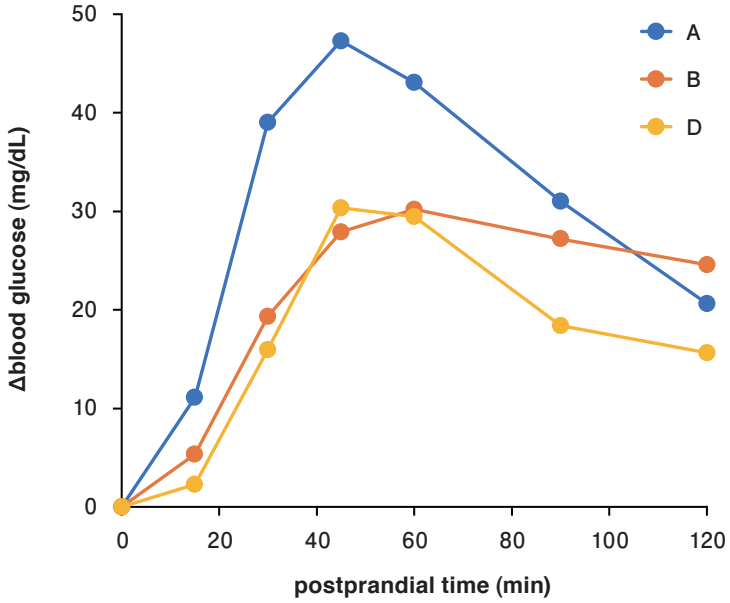

Fig. 3. **Fluctuation of the blood glucose level after the test food intake.**

A; steamed rice (150g), B; vegetable salad (undressed, 101g) before steamed rice (138g), D; yogurt (200g) before steamed rice (120g). n = 20, The figure is adapted from Reference 17.

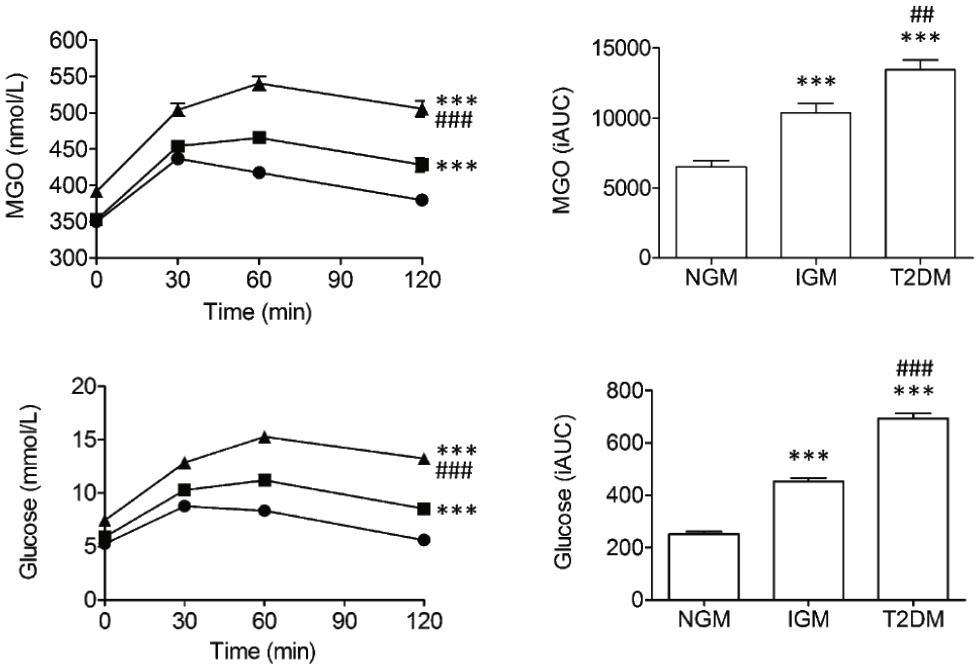

Fig. 4. **Plasma methylglyoxal and glucose levels during an OGTT.**

Methylglyoxal (MGO) levels during an OGTT over time and these data calculated as an iAUC. Data are shown as means ± SEM. ●, NGM (normal glucose metabolism), n = 279; ■, IGM (impaired glucose metabolism), n = 120; ▲, type 2 diabetes, n = 92. ***, P < 0.001 compared with NGM; ###, P < 0.001, ##, P < 0.01 compared with IGM. The figure is adapted from Reference 23.

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