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Review

Postprandial Reactive Hypoglycemia

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Abstract

Reactive hypoglycemia (RH) is the condition of postprandially hypoglycemia occurring 2-5 hours after food intake. RH is clinically seen in three different forms as follows: idiopathic RH (at 180 min), alimentary (within 120 min), and late RH (at 240–300 min). When the first-phase insulin response decreases, firstly, blood glucose starts to rise after the meal. This leads to late but excessive secretion of the second-phase insulin secretion. Thus, late reactive hypoglycemia occurs. Elevated insulin levels also cause down-regulation of the insulin post-receptor on the muscle and fat cells, thus decreasing insulin sensitivity. The cause of the increase in insulin sensitivity in IRH at 3 h is not completely clear. However, there is a decrease in insulin sensitivity in late reactive hypoglycaemia at 4 or 5 hours. Thus, patients with hypoglycemia at 4 or 5 h who have a family history of diabetes and obesity may be more susceptible to diabetes than patients with hypoglycemia at 3 h. We believe that some cases with normal glucose tolerance in OGTT should be considered as prediabetes at <55 or 60 mg/dl after 4-5 hours after OGTT. Metformin and AGI therapy may be recommended if there is late RH with IFG. Also Metformin, AGİ, TZD, DPP-IVInhibitors, GLP1RA therapy may be recommended if there is late RH with IGT. As a result, postprandial RH (<55 or 60 mg/dl), especially after 4 hours may predict diabetes. Therefore, people with RH along with weight gain and with diabetes history in the family will benefit from a lifestyle modification as well as the appropriate antidiabetic approach in the prevention of diabetes.

Keywords: AGİ; DPP-IVInhibitors; metformin; microbiota; postprandially hypoglycemia; prediabetes; reactive hypoglycaemia; TZD.

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Reactive hypoglycemia (RH) is the condition of postprandially hypoglycemia occurring 2-5 hours after food intake.[1] Many conditions are associated with postprandial hypoglycemia. RH clinically seen in three different forms as follows: idiopathic RH (at 180 min), alimentary (within 120 min) and late RH (at 240–300 min). Earliest change before type 2 diabetes is the loss of first-phase insulin release, which emerges with fasting glucose levels of about 110 mg/dl. Lack of first-phase insulin release, an excellent predictor of both types of diabetes, is thought to be the earliest sign of the adverse effects of hyperglycemia on beta-cells and insulin-sensitive tissues.[2] When the first-phase insulin response decreases, firstly, blood glucose starts to rise after the meal, which leads to late but excessive secretion of the second-phase insulin secretion. Thus, late reactive hypoglycemia occurs.[3] Elevated insulin levels also cause down-regulation of the insulin postreceptor on the muscle and fat cells, thus decreasing insulin sensitivity. The cause of the increase in insulin sensitivity in IRH at 3 h is not completely clear. However, there is a decrease in insulin sensitivity in late reactive hypoglycaemia at 4 or 5 hours. Thus, patients with hypoglycemia at 4 or 5 h who have those with a higher number of people with diabetes in the first-degree relative and who have obesity may be more susceptible to diabetes

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than patients with hypoglycemia at 3 h.

Reactive hypoglycemia is seen in prediabetic states and diabetic patient (diabetic RH), gastrointestinal dysfunction (alimentary RH), and patients with hormone deficiency states (hormonal RH). However, large patient group characterized as having idiopathic RH. The reason for alimentary, hormonal, and diabetic RH is clear, whereas the idiopathic RH is complex. Characteristic alterations in insulin secretion accompany each of these conditions. Elevated insulin levels usually account for the hypoglycemia. Some patients rarely show increased insulin sensitivity. In alimentary RH, rapid gastric emptying and increased plasma GLP-1 levels precede RH after oral glucose loading in gastrectomy patients,[4] most patients with idiopathic RH have a delayed insulin secretion that occurs inappropriately in conjunction with falling levels of plasma glucose. RH may arise from an increased insulin response, which might be related either to insulin resistance or to increased GLP-1, renal glycosuria, defects in glucagon response, or high insulin sensitivity probably the most frequently (50–70%), which is not be measured by indices of insulin sensitivity.[5] Earliest changes during the development of type 2 diabetes are the loss of first-phase insulin release, in which plasma glucose levels rise sharply after a meal.[2] Initially, this precipitates increased stimulation of second-phase insulin release, leading to late postprandial hypoglycemia as a result of elevated plasma insulin persisting after the nutrients have disappeared.[3] Therefore, late postprandial hypoglycemia (diabetic RH) occurs within the 4–6 h after food intake. Elevated insulin levels also cause down-regulation of the insulin postreceptor signals on the muscle and fat cells, thus decreases insulin sensitivity.[6]

In clinical practice, the use of OGTT may be discussed as a suboptimal method for the diagnosis of RH. Neither the OGTT nor the mixed meal test is really a suitable this diagnosis because they show false-positive and false-negative results, respectively.[7] However, the OGTT demonstrates insulin sensitivity and provides a better diagnostic approach to RH. Occurring late postprandially hypoglycemia with a family history of diabetes, even if they are lean, should be considered at potential risk of diabetes in the future in patients with late RH.

The Relationship Between Prediabetes and Reactive Hypoglycemia

Insulin secretion is secreted in phases called the first and second phases. The first phase of insulin is the rapid release of ready insulin in the first 10 minutes. Second phase insulin which is the slowly released insulin in 24 hours. Loss of first-phase insulin secretion and decreased second-phase insulin secretion are characteristic features of type 2 diabetes. In the early period of type 2 diabetes and in IGT, the first-phase insulin secretion declines with the loss.[8, 9] Depending on the loss of first-phase insulin, the relative increase in the second-phase insulin secretion is then reduced, which means that both late and hypersecretioned insulin lead to hypoglycemia. Hypoglycemia, which occurs mostly after 2-5 hours of food intake, is called postprandial reactive hypoglycemia.

Postprandial Reactive Hypoglycemia as a Prediabetic State

Prediabetes is an intermediate hyperglycaemia state with a high risk for type 2 diabetes. Every year 5-10% of the prediabetics turn into open type 2 diabetics and return to normoglycemia. The process between normal glucose metabolism and overt diabetes is called the 'prediabetic period'.[10]

Until 1997, only impaired glucose tolerance (IGT) was described as a transition from normal glucose tolerance to type 2 diabetes. A new prediabetic nomenclature was introduced after 1997 by the American Diabetes Association for type 2 non-diabetic with fasting plasma glucose between 110 and 126 mg/dl.[11] This condition was called impaired fasting glucose (IFG). Thus, before type 2 diabetes, IFG also took place after IGT. When we refer to prediabetes, there are three cases such as isolated IFG, isolated IGT and combined IFG+IGT. Those with combined IFG+IGT have a 2-fold greater risk of diabetes than those with IFG or IGT alone. The 2-hour plasma glucose from 140-199 mg/dl (Impaired glucose tolerance-IGT) between 100-125 mg/dl of IFG (impaired fasting glucose) and 2 hours of 75 g OGTT is called prediabetes.

In recent years, it has been suggested that nondiabetic patients with the metabolic syndrome criterion according to the Botnia study and OGTT 1 hour plasma glucose >155 mg/dl + ATP III are classified as low-middle-high as a risk for diabetes.[12] It has also been reported that patients with normal glucose tolerance and 1-hour blood glucose ≥155 mg/dl on OGTT cause more diabetes risk than impaired fasting glucose.[13]

Approximately 70% of the prediabetic patients who are followed for life are diabetic in the later stages of their life. Prediabetes is a sign that the risk of developing diabetes is high in the future and poses a high risk not only for diabetes but also for cardiovascular diseases. IFG and IGT are associated with obesity, dyslipidemia and hypertension.

Cardiovascular mortality is also significantly increased in prediabetic patients compared to patients with normal blood glucose.[14, 15]

Previous prospective randomized trials have shown that lifestyle modifications and pharmacological agents significantly reduce the risk of developing Type 2 DM and car-

diovascular risk factors in prediabetic patients.[16] Thus, it is important to look for new prediabetes indicators.

We have shown previously that the 4 h OGTT glucose level, but not the 3 h OGTT glucose level, was significantly correlated with insulin resistance indices, such as fasting insulin level, HOMA-IR, Quicky index, and FIRI lean subjects. These results indicate more exact insulin resistance in RH at 4 h or 5 h than in RH at 3 h.[17]

We believe that some cases with normal glucose tolerance in OGTT or cases with IGT criteria in OGTT should be considered as prediabetes at <55 mg/dl after 3 hours after OGTT is extended to 4 or 5 hours.

Insulin Resistance and Beta-cell Dysfunction in Prediabetic Reactive Hypoglycemia

Postprandial reactive hypoglycemia since it may be associated with IFG and/or IGT, it is not wrong to call such a case as prediabetic reactive hypoglycaemia. Both IFG and IGT have both insulin resistance and beta-cell defect. When we look at insulin resistance, both IFG and IGT have insulin resistance. However, the origin of insulin resistance is different. Individuals with IFG have insulin sensitivity close to normal/normal in the muscle with severe hepatic insulin resistance in the liver whereas individuals with IGT have moderate insulin resistance in the liver, but severe insulin resistance in the muscle.[9, 15-19]

Studies on hyperglycemia showed that the first and second phase of insulin secretion was significantly reduced in IGT. A recent study showed that the first phase insulin secretion was significantly reduced in both IFG and IGT, while the second phase insulin secretion was only reduced in IGT.[10, 20] An increase in the 2-hour plasma glucose level in OGTT suggests a more severe insulin resistance and beta-cell dysfunction in IGT as opposed to IFG. These results demonstrate a definite beta-cell defect in IFG and IGT.[21]

The Role of Incretins in Insulin Resistance and Beta-cell Dysfunction in Prediabetics

It has been demonstrated that the effect of incretin is impaired with no decrease in GLP-1 or GIP levels as glucose sensitivity decreases in studies of obese dysglycemic teens.[22] In contrast, another study showed a decrease response of GLP-1 to oral glucose in prediabetic patients.

In non-diabetic subjects, Incretins are responsible for 50–70% of the total insulin secreted after oral glucose administration.[23–25] The incretin effect is impaired and contributes to 20-35% of the insulin response to oral glucose, in type 2 diabetes patients.[26]

Diagnose of hypoglycemia requires blood sugar to be 55 mg/dL or less. However, symptoms of hypoglycaemia can be seen without decreasing blood sugar to 55 mg/dl, which is called postprandial syndrome.

Lupoli et al. Suggests that GLP-1 may be involved in the pathogenesis of idiopathic reactive hypoglycemia without prediabetes. Indeed, GLP-1 secretion was increased in the first 30 minutes. Insulin secretion was increased in the following 90 minutes after glucose load in IRH individuals. At the same time that there was suppression of glucagon secretion at 120-180 min and a decrease in blood glucose levels at 240 min.

It has been postulated that both impaired insulin and excessive glucagon secretion in type 2 diabetes are contributed by the "incretin defect", defined primarily as inadequate release or response to the gastrointestinal incretin hormones upon meal intake.

Incretin hormones potentiate the stimulus to insulin secretion in the postprandial period have been implicated as additional factors in the pathogenesis of type 2 diabetes. The combined actions of GLP-1 and GIP can account for most of the incretin effect in normal subjects. Recently, studies demonstrated that potential role of these peptides in the abnormal handling of glucose by splanchnic tissues and perhaps, in decline in beta-cell insulin secretion.[25–27]

Type of Postprandially Reactive Hypoglycemia

1. Early Postprandially Reactive Hypoglycemia

Early reactive hypoglycemia occurs in the first 1-2 hours of OGTT. It may be due to accelerated gastric emptying, or exaggerated incretin effect. It is also possible that accelerated gastric emptying leads to increase of incretin.[1]

Insulin secretion increases in response to oral glucose stimulation. This occurs through increased glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) and ultimately leads to hyperglycaemia with excessive insulin exocytosis and early upregulation of GLUT 4 channels. In addition to increased insulin secretion, GLP-1 by suppressing the glucagon causes an insufficient response to hypoglycemia and accelerated gastric emptying, leading to early hypoglycemia. As a result, an early-onset of reactive hypoglycemia occurs due to the incretin effect related to glucose loading occurs.[27, 28]

2. Idiopathic Postprandially Reactive Hypoglycemia

Idiopathic reactive hypoglycemia occurs at the 3rd hour of OGTT. It occurs mostly in teenagers and nonobese. The cause and pathophysiological importance have not been fully elucidated. This type of hypoglycemia usually does not develop diabetes. Tamburrano et al.[29] reported that increased insulin sensitivity represents a feature of idiopathic reactive hypoglycemia.

3. Late Postprandially Reactive Hypoglycemia

It occurs at the 3rd-5th hour of OGTT. Late reactive hypoglycemia may be partially due to insulin resistance syndrome. It is probably a cause of delayed insulin secretion. Thus, the delayed insertion of GLUT-4 may be the subject of discussion. In IGT, inhibition of first-phase insulin secretion in response to oral glucose or mixed meal resulting in an increase of blood glucose at 60-90 min compared to 90-120 may result in late reactive hypoglycemia due to an exaggerated relative increase in second phase insulin secretion. For all these reasons, late-reactive hypoglycemia may be a predictor of diabetes.[30–32]

New Definition Reactive Hypoglycemia Syndromes

1. **Long QT syndrome with reactive hypoglycemia:** Long QT, hyperinsulinemia, and low potassium after an oral glucose challenge are demonstrated in some reactive hypoglycemic patients who have mutations in KCNQ1.[33]
2. **Middleton Syndrome:** Patients with normal gastric anatomy may experience symptoms and signs, such as postprandial reactive hypoglycemia, early satiety and diarrhea, due to primary accelerated gastric emptying.[34, 35]

Treatment approach in postprandially reactive hypoglycemia: Postprandial reactive hypoglycemia should be treated accordingly either alone or together with IFG and/or IGT (Table 1).

Alpha Glucosidase Inhibitors

Inhibitors of α-glucosidase (acarbose and miglitol) can reduce the levels of GIP, which is released from K cells in the duodenum, which can be stimulated through the absorption of carbohydrates and fat. GIP increases significantly after the excessive ingestion of nutrients. There are studies that showed that he GIP and glucagon levels decreased after a mixed meal in patients with new diagnosed type 2 diabetics by treatment with single-dose acarbose[36, 37] and acarbose decreased GIP and glucagon only in a mixed meal test rather than OGTT.[38]

Glitazones

Low-dose glitazones given to patients with reactive hypoglycemia associated with IGT are also considered to be effective in the symptoms of reactive hypoglycaemia and the prevention of diabetes.[39, 40] As a matter of fact, hyperinsulinemia and IGT were found in OGTT in 2 cases with hypoglycemic symptoms, and it has been shown that hyperinsulinemic clamp reduces the insulin sensitivity. In these cases, hypoglycaemic symptoms of IGT improved after the use of 15 mg pioglitazone. It has been reported that low dose of 15 mg pioglitazone prevents reactive hypoglycemia in impaired glucose tolerance.[41]

Table 1. OAD Drug therapy in IFG and IGT with postprandial reactive hypoglycaemia

IFG + Postprandial reactive hypoglycemia: Metformin, AGI
IGT + Postprandial reactive hypoglycemia: Metformin, AGİ, TZD, DPP-IV Inhibitors, GLP1RA

Incretins

DPP-IV inhibitors have been suggested to be involved in the treatment of prediabetes.[43] Glucagon levels decreased in GLP-1 compared to placebo and with a 32% reduction in postprandial glucose excursions no evidence of hypoglycemia or weight gain was seen in studies with single dose 50 mg vildagliptin. This effect suggests that it may be used in the treatment of reactive hypoglycaemia, possibly in prediabetic patients, and may prevent both the symptoms of hypoglycaemia and diabetes.[44]

Dipeptidyl peptidase-4 (DPP-4) inhibitors improve insulin secretion and reduces glucagon secretion, thereby reducing hyperglycaemia. These incretin effects are glucose-dependent, thus minimize the risk of hypoglycaemia. Incretin-based therapies are of interest in subjects with mild postprandial glycaemic excursions but without overt T2DM. Sitagliptin treatment for 7–8 weeks resulted in reductions in post-challenge glucose excursions during both an MTT and an OGTT, in Japanese subjects with IGT. The observation that treatment with sitagliptin increased the early insulin response to the glucose load during the OGTT, and reduced circulating glucagon levels during the MTT.[45]

It is suggested that the incretin-based treatments are promising in both IFG and IGT treatment, and we think that DPP-IV inhibitors may be useful in prediabetic patients, especially in postprandial reactive hypoglycaemia.[50] Also, GLP-1 receptor agonist is likely to have a preventive effect on postprandial reactive hypoglycemia with prediabetes, especially in overweight people. It has been suggested that pathophysiologic- based therapy is associated with marked improvement in glucose tolerance and reversion of prediabetes to normal glucose tolerance in more than 50% of patients.[44-47]

Gut Microbiome

Recently, the gut microbiota has been discussed as a potential target for the control of diabetes and reactive hypoglycaemia, and the possibility to correct gut microbiota dysbioses through diet. The macrobiotic Ma-Pi 2 diet, with its high fibre load, was effective in increasing the production of SCFAs by the gut microbiota. The macrobiotic Ma-Pi 2 diet reduced blood glucose excursions during the day, thereby facilitating glycemic control in subjects with RH.[48, 49] Thus, these SCFA metabolites are preventive, reactive hypoglycemia.

Conclusion

As a result, biochemical hypoglycaemia during 4h or 5h OGTT in the absence of diabetes may possibly be associated with insulin resistance. Postprandial reactive hypoglycaemia without diabetes, especially after 4 or 5 hours, may predict reactive hypoglycaemic diabetes. Therefore, people with reactive hypoglycaemia along with weight gain and, with diabetes history in the family will benefit from a lifestyle modification as well as the appropriate antidiabetic approach in the prevention of diabetes.

Disclosures

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