SJIF Impact Factor: 5.464

WORLD JOURNAL OF ADVANCE HEALTHCARE RESEARCH

ISSN: 2457-0400
Volume: 8.
Issue: 2
Page N. 143-147
Year: 2024

Review Article www.wjahr.com

REACTIVE HYPOGLYCEMIA AND ITS CLINICAL IMPORTANCE

***[1]Dr. R. Anil Kumar and [2]Dr. Surekha B. Shetty**

[1]Professor and HOD Diabetes and Endocrinology, Karnataka Institute of Endocrinology and Research, Bangalore.
[2]Professor, Karnataka Institute of Endocrinology and Research, Bangalore.

Article Received date: 26 November 2023 **Article Revised date:** 16 December 2023 **Article Accepted date:** 06 January 2024

***Corresponding Author: Dr. R. Anil Kumar**

Professor and HOD Diabetes and Endocrinology, Karnataka Institute of Endocrinology and Research, Bangalore.

Reactive hypoglycemia (RH) is the condition of postprandial hypoglycemia occurring 2-5 hours after food intake.[1] It is clinically seen in three different forms as follows.

1. Idiopathic reactive hypoglycemia. (at 180 min)
2. Alimentary reactive hypoglycemia. (within 120 min)
3. Late reactive hypoglycemia (240–300 min)

The symptoms of reactive hypoglycemia generally start within 4 hours after a meal. They can include anxiety, blurry vision, racing heart, confusion, dizziness, irritability, headache, hunger, light-headedness, sweating, shaking, trouble sleeping, feeling faint, extreme tiredness and weakness.

The occurrence of reactive hypoglycemia is related to abnormal insulin secretion. Insulin secretion occurs in phases called the first and second phases. The first phase of insulin refers to the rapid release of ready insulin in the first 10 minutes. Second phase insulin refers to the slowly released insulin over 24 hours. Loss of first-phase insulin secretion and decreased second-phase insulin secretion are characteristic features of type 2 diabetes. In the early phase of type 2 diabetes and IGT, the first-phase insulin secretion declines. When the first-phase insulin response decreases, blood glucose starts to rise after the meal. This in turn, leads to late but excessive secretion of the second-phase insulin secretion and the mismatch leads to late reactive hypoglycemia.[2,3]

Prediabetes and Reactive hypoglycemia

Prediabetes is an intermediate hyperglycaemia state with a high risk for type 2 diabetes. Every year, 5-10% of the people with prediabetes convert to type 2 diabetes. The state between normal glucose metabolism and overt diabetes is called the 'prediabetic state'.[4]

There are 3 different groups of prediabetes

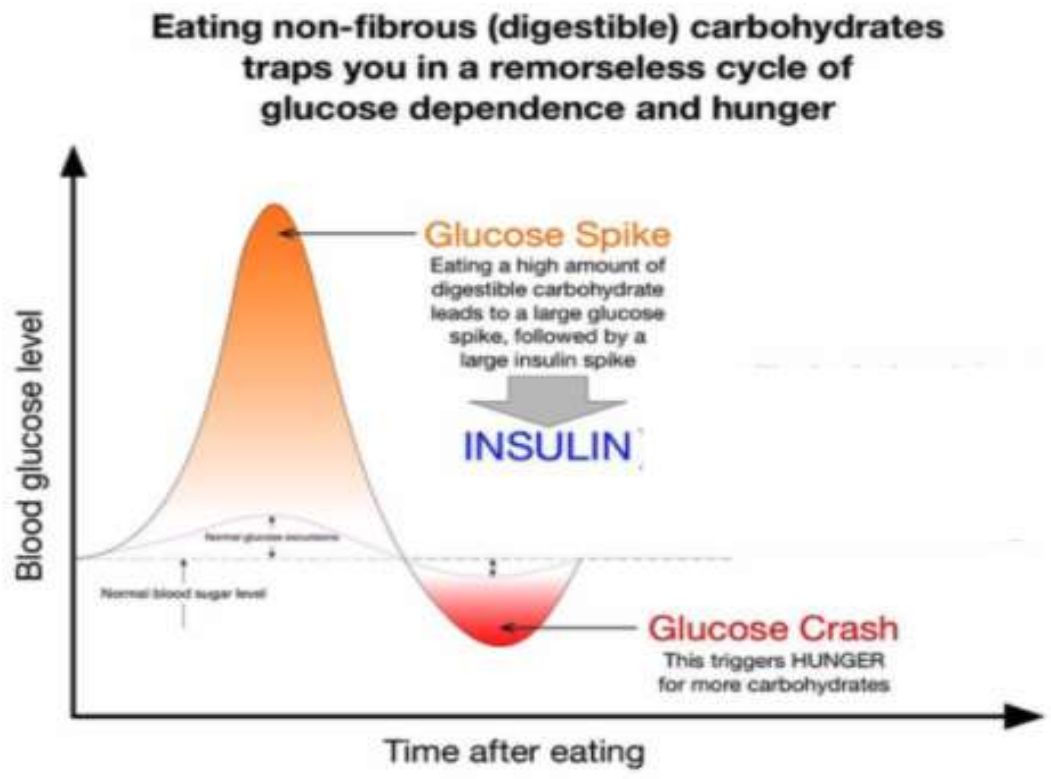
1. IFG- Fasting plasma glucose – 100 to 125 mg/dl.
2. IGT – Post prandial plasma glucose after 75 gm OGTT – 140 to 199 mg/dl.
3. HBA1C – 5.7 to 6.4%.

Those with combined IFG+IGT have a 2-fold greater risk of diabetes than those with IFG or IGT alone. Cardiovascular mortality is also significantly increased in prediabetic patients compared to patients with normal blood glucose.[5,6] Previous prospective randomized trials have shown that lifestyle modifications and pharmacological agents significantly reduce the risk of developing type 2 diabetes and cardiovascular risk factors in prediabetic patients.[7]

Both IFG and IGT have coexisting insulin resistance and beta-cell defect. It is of interest to note that both IFG and IGT have insulin resistance, but, 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.[7-11] 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.[12]

Postprandial reactive hypoglycemia being associated with IFG and/or IGT could also be called as prediabetic reactive hypoglycaemia. Reactive hypoglycemia is symptomatic, and occurs due to an abnormally rapid rise in blood glucose after eating, followed by an equally steep crash. It occurs repeatedly in affected individuals, and is considered a prediabetic state. While it is thought

to be due to discordance between insulin and glucose, or insulin and glucagon levels, the exact pathogenic mechanism is uncertain.



Here are examples of foods that may cause reactive hypoglycemia

- Foods with high amounts of added sugar + highly processed flour - a large donut, pastries.
- Large quantity of minimal fiber foods- rice with no protein or veggies, big bowl of rice krispies or frosted flakes, stack of pancakes.
- Liquid carbohydrates - juices, regular soda.

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 are 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.[13]

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.[14]

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.[15] 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.[16] 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.[17]

Types of Postprandial Reactive Hypoglycemia

1. Early Postprandial 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.[18,19]

2. Idiopathic Postprandial 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.[20] reported that increased insulin sensitivity represents a feature of idiopathic reactive hypoglycemia.

3. Late Postprandial 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.[21,22,23]

Five hour OGTT with estimation of blood glucose and insulin levels every one hour may help to diagnose early and late reactive hypoglycemia

Management

Management of hypoglycemia begins with immediate measures to correct hypoglycemia immediately with oral or intravenous glucose**.** Patient education is crucial for recognizing the symptoms of hypoglycemia early and correcting it. They should be advised to monitor their capillary blood glucose by a glucose meter, when symptomatic. Family members should also be educated to be aware of hypoglycemic symptoms and the use of glucagon injection in case of severe hypoglycemia. Long term management includes dietary modifications and pharmacotherapy.

Dietary Modifications

1. **Low-carbohydrate diet and/or frequent small meals is the first treatment of this condition**. The first important point is to add small meals at the middle of the morning and of the afternoon, when glycemia would start to decrease.
2. **Limiting the intake of sugary foods and beverages, such as desserts, sweet tea, and fruit juices:** These foods can trigger an excessive increase in insulin, which can result in a quick drop in blood sugar.
3. **Including lean protein and healthful fats in the diet:** Examples of lean protein include fish and skinless poultry, while examples of healthful fats include avocados and olive oil.
4. **Eating high-fiber foods:** These include fruits, vegetables, beans, and whole grains.
5. **Limiting or avoiding alcohol:** Alcohol can cause low blood sugar. If a person wishes to drink alcohol, it is best to do so in small amounts and to eat something alongside it.
6. **Limiting or avoiding caffeine:** Coffee, tea, and some sodas contain caffeine. This stimulant can cause the same symptoms of low blood sugar.

Tips to prevent sugar crashes due to reactive hypoglycemia include

1. Exercising regularly, as exercise increases cellular sugar uptake, which decreases excessive insulin release.
2. Avoiding eating meals or snacks composed entirely of carbohydrates. It is ideal to simultaneously ingest fats and proteins, which have slower rates of absorption.
3. Consistently choosing longer lasting, complex carbohydrates to prevent rapid blood-sugar dips in the event that one does consume a disproportionately large amount of carbohydrates with a meal.
4. Monitoring any effects of medications.

Pharmacotherapy

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

1. **Acarbose:** It is an α-glucosidase inhibitor and acts by delaying the intestinal breakdown of complex carbohydrate to glucose, thus reducing postprandial glucose and insulin surge and subsequent hypoglycaemia A study involving 21 non-obese patients complaining of postprandial hypoglycemia and had blood glucose values of < 54 mg/dl on one or more occasions during a 5 h oral glucose tolerance test (OGTT) showed that, after 3 months of acarbose treatment, the lowest plasma glucose levels at the 3rd and 4th hours increased to 67 mg/dI and 75 mg/dI respectively. Plasma insulin and c-peptide levels were reduced between the 1st and 5th hours, but only the 1st and 2nd hour decrements were statistically significant.[24]
2. **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.[25,26] In cases with hypoglycemic symptoms and IGT, symptoms improved after the use of 15 mg pioglitazone. Studies have reported that low dose of 15 mg pioglitazone prevents reactive hypoglycemia in impaired glucose tolerance.

3. **Dipeptidyl peptidase-4 (DPP-4) inhibitors:** DPP-IV inhibitors improve insulin secretion and reduce glucagon secretion, thereby reducing hyperglycaemia. These incretin effects are glucose-dependent, thus minimize the risk of hypoglycaemia. DPP-4 inhibitors are known to increase early insulin response and reduce circulating glucagon levels during an OGTT and mixed-meal tolerance test (MTT), respectively.[27,28] These effects are known to be glucose dependent and minimize both hyper- and hypoglycemia.[27] A double-blind, parallel-group study of Japanese patients with impaired glucose tolerance treated for 7–8 weeks with Sitagliptin significantly reduced glucose excursions during both an MTT and an OGTT. The effect was associated with an increase in early insulin secretion after oral glucose loading, as well as a blunted glucagon response during an MTT.[28] Sitagliptin was recently evaluated in a randomized, double-blind, placebo-controlled clinical trial, in which it was found to improve first-phase insulin secretion and reduce postprandial hypoglycemia.[29]
4. **Use of combination treatment with a DPP-4 inhibitor and an α-glucosidase inhibitor**: the combination has been found to be useful for idiopathic postprandial RH refractory to lifestyle intervention and α-glucosidase inhibitor treatment.[30] α-Glucosidase inhibitors (acarbose and miglitol) reduce levels of both GIP and glucagon[31], delay glucose absorption, and thereby blunt the insulin response to glucose.[32] DPP-4 inhibitors are known to increase the early insulin response (by increasing circulating concentrations of active GLP-1), reduce glucagon secretion in a glucose-dependent manner, and therefore reduce both hyper- and hypoglycemia.
5. **Gut Microbiota:** gut microbiota has been discussed as a potential target for the control of diabetes and also reactive hypoglycaemia, by correcting gut microbiota dysbiosis through diet. The Ma-Pi 2 diet is a low-fat, high-fiber, high-complex carbohydrate, mainly vegetarian diet that was specifically designed for intensive treatment of T2D patients. The macrobiotic Ma-Pi 2 diet, with its high fiber 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.[33,34]

CONCLUSION

Postprandial reactive hypoglycaemia is a common phenomenon. The presence of postprandial hypoglycemia requires an investigation to determine the specific cause of hypoglycemia. It will benefit from a lifestyle modification as well as the appropriate antidiabetic medications.

Abbreviations
RH-Reactive hypoglycemia.
IFG-Impaired fasting glucose tolerance.
IGT-Impaired glucose tolerance,
OGTT-Oral glucose tolerance test.
GLUT – Glucose transporter.

REFERENCES

1. Brun JF, Fedou C, Mercier J. Postprandial reactive hypoglycemia. Diabetes Metab, 2000; 26: 337–51.
2. Wasada T, Kuroki H, Katsumori K, Arii H, Sato A, Aoki K. Who are more insulin resistant, people with IFG or people with IGT? Diabetologia, 2004; 4.
3. Pimenta WP, Santos ML, Cruz NS, Aragon FF, Padovani CR, Gerich JE. Brazilian individuals with impaired glucose tolerance are characterized by impaired insulin secretion. Diabetes Metab, 2002; 28: 468–76.
4. Tabák AG, Herder C, Rathmann W, Brunner EJ, Kivimäki M. Prediabetes: a high-risk state for diabetes development. Lancet, 2012; 379: 2279–90.
5. Ford ES, Zhao G, Li C. Pre-diabetes and the risk for cardiovascular disease: a systematic review of the evidence. J Am Coll Cardiol, 2010; 55: 1310–7.
6. Festa A, D'Agostino R Jr, Hanley AJ, Karter AJ, Saad MF, Haffner SM. Differences in insulin resistance in nondiabetic subjects with isolated impaired glucose tolerance or isolated impaired fasting glucose. Diabetes, 2004; 53: 1549–55.
7. Godsland IF, Jeffs JAR, Johnston DG. Loss of beta cell function as fasting glucose increases in the non-diabetic range. Diabetologia, 2004; 47: 1157–66.
8. Festa A, D'Agostino R Jr, Hanley AJ, Karter AJ, Saad MF, Haffner SM. Differences in insulin resistance in nondiabetic subjects with isolated impaired glucose tolerance or isolated impaired fasting glucose. Diabetes, 2004; 53: 1549–55.
9. Altuntas Y, Bilir M, Ucak S, Gundogdu S. Reactive hypoglycemia in lean young women with PCOS and correlations with insulin sensitivity and with beta cell function. Eur J Obstet Gynecol Reprod Biol, 2005; 119: 198–205. [CrossRef]
10. Weyer C, Bogardus C, Pratley RE. Metabolic characteristics of individuals with impaired fasting glucose and/or impaired glucose tolerance. Diabetes, 1999; 48: 2197–203. [CrossRef]
11. Meyer C, Pimenta W, Woerle HJ, Van Haeften T, Szoke E, Mitrakou A, et al. Different mechanisms for impaired fasting glucose and impaired postprandial glucose tolerance in humans. Diabetes Care, 2006; 29: 1909–14.
12. Van Haeften TW, Pimenta W, Mitrakou A, Korytkowski M, Jenssen T, Yki-Jarvinen H, et al. Disturbances in beta-cell function in impaired fasting glycemia.
13. Gebhard B, Holst JJ, Biegelmayer C, Miholic J. Postprandial GLP1, norepinephrine, and reactive hypoglycemia in dumping syndrome. Dig Dis Sci, 2001; 46: 1915–23.

14. Leonetti F, Foniciello M, Iozzo P, Riggio O, Merli M, Giovannetti P, et al. Increased nonoxidative glucose metabolism in idiopathic reactive hypoglycemia. Metabolism, 1996; 45: 606–10.
15. Poitout V, Robertson RP. An integrated view of beta-cell dysfunction in type-II diabetes. Annu Rev Med, 1996; 47: 69–83.
16. Mitrakou A, Kelley D, Mokan M, Veneman T, Pangburn T, Reilly J, et al. Role of reduced suppression of glucose production and diminished early insulin release in impaired glucose tolerance. N Engl J Med, 1992; 326: 22–9.
17. Mandarino L, Baker B, Rizza R, Genest J, Gerich J. Infusion of insulin impairs human adipocyte glucose metabolism in vitro without decreasing adipocyte insulin receptor binding. Diabetologia, 1984; 27: 358–63.
18. Lupoli R, Cotugno M, Griffo E, Nosso G, Riccardi G, Capaldo B. Role of the Entero-Insular Axis in the Pathogenesis of Idiopathic Reactive Hypoglycemia: A Pilot Study. J Clin Endocrinol Metab, 2015; 100: 4441–6.
19. Vilsbøll T, Krarup T, Madsbad S, Holst JJ. Both GLP-1 and GIP are insulinotropic at basal and postprandial glucose levels and contribute nearly equally to the incretin effect of a meal in healthy subjects. Regul Pept, 2003; 114: 115–21.
20. Tamburrano G, Leonetti F, Sbraccia P, Giaccari A, Locuratolo N, Lala A. Increased insulin sensitivity in patients with idiopathic reactive hypoglycemia. J Clin Endocrinol Metab, 1989; 6.
21. Cederholm J, Wibell L. Insulin release and peripheral sensitivity at the oral glucose tolerance test. Diabetes Res Clin Pract, 1990; 10: 167–75. [CrossRef]
22. Abdul-Ghani MA, Jenkinson CP, Richardson DK, Tripathy D, DeFronzo RA. Insulin secretion and action in subjects with impaired fasting glucose and impaired glucose tolerance: results from the Veterans Administration Genetic Epidemiology Study. Diabetes, 2006; 55: 1430–5.
23. Altuntas Y, Yener Ozturk F. The importance of prediabetes and therapeutic approach. Med Bull Sisli Etfal Hosp, 2015; 49: 238–42.
24. Ozgen AG, Hamulu F, Bayraktar F, Cetínkalp S, Yilmaz C, Túzún M, Kabalak T. Long-term treatment with acarbose for the treatment of reactive hypoglycemia. Eat Weight Disord, 1998 Sep; 3(3): 136-40. doi: 10.1007/BF03340001. PMID: 10728163.
25. Luo Y, Paul SK, Zhou X, Chang C, Chen W, Guo X, et al. Rationale, Design, and Baseline Characteristics of Beijing Prediabetes Reversion Program: A Randomized Controlled Clinical Trial to Evaluate the Efficacy of Lifestyle Intervention and/or Pioglitazone in Reversion to Normal Glucose Tolerance in Prediabetes. J Diabetes Res, 2017; 2017: 7602408.
26. Espinoza SE, Wang CP, Tripathy D, Clement SC, Schwenke DC, Banerji MA, et al. Pioglitazone is equally effective for diabetes prevention in older versus younger adults with impaired glucose tolerance. Age (Dordr), 2016; 38: 485–93.
27. Altuntaş Y. Postprandial reactive hypoglycemia. *Sisli Etfal Hastan Tip Bul*, 2019; 53: 215–220.
28. Vella A, Bock G, Giesler PD, et al. Effects of dipeptidyl peptidase-4 inhibition on gastrointestinal function, meal appearance, and glucose metabolism in type 2 diabetes. *Diabetes*, 2007; 56: 1475–1480.
29. Kaku K, Kadowaki T, Terauchi Y, et al. Sitagliptin improves glycaemic excursion after a meal or after an oral glucose load in Japanese subjects with impaired glucose tolerance. *Diabetes Obes Metab*, 2015; 17: 1033–1041.
30. Broome DT, Kodali A, Phillips D, Makin V, Mendlovic D, Zimmerman RS. Combined Dipeptidyl Peptidase 4 Inhibitor and α-Glucosidase Inhibitor Treatment in Postprandial Hypoglycemia. Clin Diabetes, 2022 Jan; 40(1): 116-119. doi: 10.2337/cd21-0042. PMID: 35221483; PMCID: PMC8865782.
31. Chen Z, Fu X, Kuang J, et al. Single-dose acarbose decreased glucose-dependent insulinotropic peptide and glucagon levels in Chinese patients with newly diagnosed type 2 diabetes mellitus after a mixed meal. *BMC Endocr Disord*, 2016; 16: 55.
32. Middleton SJ, Balan K. Idiopathic accelerated gastric emptying presenting in adults with post-prandial diarrhea and reactive hypoglycemia: a case series. *J Med Case Reports*, 2012; 6: 132.
33. Quercia S, Turroni S, Fiori J, Soverini M, Rampelli S, Biagi E, et al. Gut microbiome response to short-term dietary interventions in reactive hypoglycemia subjects. Diabetes Metab Res Rev, 2017; 33.
34. Soare A, Khazrai YM, Fontana L, Del Toro R, Lazzaro MC, Di Rosa C, et al. Treatment of reactive hypoglycemia with the macrobiotic Ma-pi 2 diet as assessed by continuous glucose monitoring: The MAHYP randomized crossover trial. Metabolism, 2017; 69: 148–56.