Hyperinsulinemia

Subjects: Pathology

Contributor: Joseph Janssen

For many years, the dogma has been that insulin resistance precedes the development of hyperinsulinemia. However, recent data suggest a reverse order and place hyperinsulinemia mechanistically upstream of insulin resistance. Genetic background, consumption of the “modern” Western diet and over-nutrition may increase insulin secretion, decrease insulin pulses and/or reduce hepatic insulin clearance, thereby causing hyperinsulinemia. Hyperinsulinemia disturbs the balance of the insulin–GH–IGF axis and shifts the insulin : GH ratio towards insulin and away from GH. This insulin–GH shift promotes energy storage and lipid synthesis and hinders lipid breakdown, resulting in obesity due to higher fat accumulation and lower energy expenditure. Hyperinsulinemia is an important etiological factor in the development of metabolic syndrome, type 2 diabetes, cardiovascular disease, cancer and premature mortality.

Keywords: hyperinsulinemia ; insulin resistance ; insulin secretion ; insulin clearance ; growth hormone ; insulin-like growth factor-I ; obesity ; diabetes ; cardiovascular disease ; cancer ; longevity

1. Introduction

Subjects with insulin resistance and hyperinsulinemia are at high risk of developing obesity, type 2 diabetes, cardiovascular disease, cancer and premature mortality [1][2][3][4][5][6][7][8][9]. The dogma has been for many years that insulin resistance is first and precedes hyperinsulinemia and type 2 diabetes mellitus. In this view, hyperinsulinemia was secondary and represented a compensatory mechanism to overcome systemic (peripheral) insulin resistance [10]. Insulin resistance was considered to be the primary etiological factor in the development of obesity, type 2 diabetes, cardiovascular disease and cancer, whereas the compensatory hyperinsulinemia was thought to be a direct consequence of insulin resistance [11]. However, recently the correctness of this view has been called into question [12][13][14]. It has even been proposed that hyperinsulinemia per se is primary and causes (and is not a consequence of) insulin resistance [13]. In this new concept, insulin resistance is proposed to be a physiological defense mechanism of the body that tries to prevent the development of hypoglycemia and to protect critical tissues from metabolic stress and nutrient-induced injury [15][16]. This opens the possibility that (early) interventions able to normalize/reduce plasma insulin concentrations might play a key role in the prevention and treatment of obesity, type 2 diabetes, cardiovascular disease, cancer and premature mortality [10][17].

2. How to Define Circulating Hyperinsulinemia

Diagnosing hyperinsulinemia is not easy in clinical practice. There is no precise and universally accepted definition of hyperinsulinemia [18]. When cut-offs are available for hyperinsulinemia, these are in most cases based on fasting insulin levels [19]. The “normal” range of fasting insulin in healthy subjects varies considerably between labs, but has been reported to vary in a range between 3 and 30 µU/mL (18–180 pmol/L) [19]. In the National Health and Nutrition Examination Surveys (NHANES), fasting circulating insulin levels in healthy adult persons have been reported to be in a range between approx. 25 and 70 pmol/L [20]. Many studies define hyperinsulinemia based on arbitrarily chosen cut-off fasting insulin concentrations or 2 h insulin concentrations after an oral glucose load (for example, >67th percentile, >75th percentile or >90th percentile for non-diabetic subjects) [21][22]. In addition, as discussed above, laboratory standardization of insulin measurements remains a problem. It has been found that serum insulin measurement with different assays shows maximal 1.8-fold variation and therefore caution should be exercised when comparing results of insulin levels from different research labs/studies [23]. Moreover, differences in the circumstances of blood sampling and handling of blood samples before the actual measurement of insulin may further play a role in the variation of insulin measurements [3].

3. Loss of Pulsatile Insulin Secretion Contributes to Insulin Resistance

In healthy subjects, insulin secretion into the circulation is pulsatile and normally accounts for 75% of the daily insulin secretion [24]. It has been proposed that pulsatile insulin release may avoid the downregulation of (hepatocyte) insulin receptors compared to the constant delivery of insulin [25]. Prolonged near-physiological pulsatile insulin infusion has a greater hypoglycemic effect than continuous insulin infusion [26]. Moderate pulsatile hyperinsulinemia in nondiabetic human subjects does not induce insulin insensitivity [26]. This is in contrast to what is found after continuous hyperinsulinemia [26]. It has been demonstrated that hyperinsulinemia produced by continuous infusion of insulin (which increased plasma insulin concentrations to levels similar to those observed in insulin-resistant conditions) can produce insulin resistance (decreased insulin receptor sensitivity), and this decrease in insulin action may occur at the receptor and post-receptor level of the insulin receptor and is tissue-specific [27]. The loss of pulsatile insulin secretion is an early feature in the development of type 2 diabetes and may be involved in the (patho)genesis of insulin resistance in a variety of circumstances [27][28]. Intravenous delivery of insulin in a constant versus pulsatile pattern led to delayed activation of hepatic insulin receptor substrate (IRS)-1 and IRS-2 signaling, impaired activation of downstream insulin signaling effector molecules AKT and Foxo1, and decreased expression of glucokinase, suggesting that the physiological pulsatile pattern of insulin delivery is important for normal hepatic insulin signaling and glycemic control and essential to preserve insulin sensitivity [29]. In addition, several lines of evidence suggest that the pattern of insulin secretion by the pancreas determines hepatic insulin clearance: the liver preferentially extracts insulin delivered in pulses [30]. Therefore, the pulse mass of insulin release dictates both hepatic (directly) as well as extrahepatic (peripheral) insulin delivery [30]. Animal studies have also demonstrated the importance of pulsatile insulin delivery in the development of insulin resistance [16]. Although an acute rise in insulin is stimulatory for the insulin receptor, persistently and continuously elevated insulin levels desensitize the insulin receptor through multiple mechanisms, both at receptor and post-receptor level [12][31][32][33]. Continuous and long-term exposure to insulin causes a reduction in the number of insulin receptors at the cellular surface by promoting internalization as well as degradation of insulin receptors [31]. With continuous and long-term exposure to insulin, the kinase activity of the insulin receptor diminishes, probably because of combined effects of phosphorylation on serine residues on the insulin receptor, the dephosphorylation of tyrosines by the action of phosphatases, and the binding of inhibitory molecules [12][34][35][36][37]. All of these effects downregulate insulin receptor signaling and thereby cause insulin resistance.

4. Hyperinsulinemia Precedes Insulin Resistance

In healthy subjects, plasma glucose is maintained within narrow ranges by a classic negative feedback system [38]. After meals, insulin secretion by the pancreas is stimulated by a rise in glucose and this brings plasma glucose back to baseline [38]. In this negative feedback system, insulin secretion is controlled and glucose levels remain within the normal range as long as subjects are able to overcome insulin resistance by increasing insulin secretion [38]. However, as soon as subjects have lost this ability, they will progress to impaired glucose tolerance and/or type 2 diabetes [38]. Until very recently, the prevailing view was that insulin resistance (that is, resistance to insulin's role in promoting glucose uptake by muscle and fat cells) preceded and caused hyperinsulinemia [39]. In this view, insulin resistance was the initial defect leading to the development of metabolic syndrome, hyperglycemia and type 2 diabetes after years or even decades later [40]. However, in genome-wide association studies (GWAS), only a few loci point to insulin resistance as the primary cause of type 2 diabetes, while the majority of the loci identified by GWAS point towards defects of the β-cell of the pancreas [41][42]. This raises the distinct possibility that a β-cell defect in insulin secretion that initially causes inappropriate hypersecretion of insulin at basal plasma glucose concentrations may be a driver of insulin resistance by insulin-induced downregulation of insulin receptors [13][16]. It is important to realize that the actual diagnostic criteria for normal glucose tolerance, impaired glucose tolerance and type 2 diabetes are not defined on the basis of pathophysiological abnormalities [43]. Thus, although cross-sectional studies have postulated that insulin secretion follows an inverted U-pattern (also termed Starling's curve of the pancreas) during natural progression from normal glucose tolerance to impaired glucose tolerance and type 2 diabetes [34], it has been repeatedly reported that a large part of individuals with normal glucose tolerance already show hyperinsulinemia before the development of impaired glucose tolerance/obesity. For example, Ferrannini et al. found increased plasma insulin levels in subjects with normal or near normal glucose tolerance [43]. In addition, it is difficult to understand how insulin resistance in subjects with normal glucose tolerance could be responsible for increased insulin secretion when blood glucose concentrations are still within the normal range. This is another argument against a primary role for insulin resistance-mediated hyperinsulinemia [44]. In addition, if fat cells were already resistant to insulin in the early phase, it is difficult to understand how hyperinsulinemia could stimulate lipogenesis and induce obesity by driving calories into fat cells [45]. Recently, a new model has been brought forward: in this new model, hyperinsulinemia is considered the primary event that secondarily causes insulin resistance and type 2 diabetes [12][44]. In support of this new model, insulin secretion has been found to be elevated before the development of hyperglycemia in a longitudinal study of

Rhesus monkeys, developing a form of type 2 diabetes, which appears to be very similar to that found in humans [46]. In addition, an increasing number of human studies support the hypothesis that basal hyperinsulinemia is primary and that it contributes secondarily to insulin resistance and many diseases and conditions [12].

In another study, half of the 4485 subjects showed hyperinsulinemia despite normal glucose clearance, suggesting that hyperinsulinemia likely occurs as a “silent disease” in a substantial proportion of an otherwise healthy population [47]. In Pima Indians with normal glucose tolerance, evidence was found that fasting hyperinsulinemia itself, independent of a low rate of insulin-stimulated glucose uptake, predicted the cumulative incidence of type 2 diabetes during a 7 year follow-up [48]. Therefore, the authors concluded that high fasting plasma insulin concentrations were not a reflection of insulin resistance but rather the consequence of a basal hypersecretion of insulin relative to the degree of insulin resistance [48]. In a fourth study, the prevalence of insulin hypersecretion in nondiabetic, normotensive obese women exceeded the prevalence of insulin resistance, which was relatively low [49].

5. How Can Hyperinsulinemia Be Modified?

In humans, there are at present three main strategies to prevent and manage hyperinsulinemia: reducing calorie intake, increasing hepatic insulin clearance and maximizing insulin sensitivity [50]. However, at this moment it is unclear which strategy is the best for preventing/managing hyperinsulinemia. Any dietary approach that causes weight loss improves hyperinsulinemia as body fat can only be stored, rather than oxidized in the presence of high insulin levels [50]. Only a few studies have studied the direct specific effects of a diet on hyperinsulinemia. Although a carbohydrate-restricted Mediterranean diet theoretically may confer the best effects, further research is needed to determine which diet is the best to modify hyperinsulinemia [50]. Studies during short-term very low calorie diets (VLCD) have found an increased hepatic insulin clearance and decline in plasma insulin concentrations, supporting that hepatic insulin clearance can be increased by energy restriction [51]. Furthermore, energy restriction induced by Roux-en-Y gastric bypass increased hepatic insulin clearance in obese subjects with normal glucose tolerance within 1 week [52]. Thus, insulin clearance can be modified within days by reducing energy intake. The early increases in insulin clearance after reduced energy intake result in metabolic changes typical for fasting (i.e., increased lipolysis and free fatty acid oxidation and a lower hepatic triglyceride content independent of weight loss) [53]. Interestingly, pharmacological lowering of hepatic triglyceride content in type 2 diabetes by rosiglitazone, a PPARγ receptor agonist, is also associated with a significant increase in insulin clearance within 16 weeks, and this effect is present without significant weight loss [54]. The pattern of food intake may also be important to reduce insulin levels. Five weeks of early time restricted feeding (6-hr feeding period during the day, with dinner before 3 pm) reduced insulin levels and improved β-cell responsiveness, insulin sensitivity, blood pressure and oxidative stress in prediabetic men even without weight loss [55]. Regular physical activity improves the whole-body metabolic health and can play a key role in the prevention and control of hyperinsulinemia, insulin resistance, prediabetes, type 2 diabetes and diabetes-related complications [56]. In a rodent study, exercise training prevented basal as well as glucose challenged insulin levels induced by a high-energy diet [57]. Two weeks of high-intensity interval or moderate-intensity continuous training improved β-cell function in people with prediabetes and type 2 diabetes [58][59].

References

1. Lakka, H.M.; Lakka, T.A.; Tuomilehto, J.; Sivenius, J.; Salonen, J.T. Hyperinsulinemia and the risk of cardiovascular death and acute coronary and cerebrovascular events in men: The Kuopio Ischaemic Heart Disease Risk Factor Study. Arch. Int. Med. 2000, 160, 1160–1168.
2. Despres, J.P.; Lamarche, B.; Mauriege, P.; Cantin, B.; Dagenais, G.R.; Moorjani, S.; Lupien, P.J. Hyperinsulinemia as an independent risk factor for ischemic heart disease. N. Engl. J. Med. 1996, 334, 952–957.
3. Pyorala, M.; Miettinen, H.; Laakso, M.; Pyorala, K. Hyperinsulinemia predicts coronary heart disease risk in healthy middle-aged men: The 22-year follow-up results of the Helsinki Policemen Study. Circulation 1998, 98, 398–404.
4. Sigal, R.J.; El-Hashimy, M.; Martin, B.C.; Soeldner, J.S.; Krolewski, A.S.; Warram, J.H. Acute postchallenge hyperinsulinemia predicts weight gain: A prospective study. Diabetes 1997, 46, 1025–1029.
5. Odeleye, O.E.; de Courten, M.; Pettitt, D.J.; Ravussin, E. Fasting hyperinsulinemia is a predictor of increased body weight gain and obesity in Pima Indian children. Diabetes 1997, 46, 1341–1345.
6. Balkau, B.; Kahn, H.S.; Courbon, D.; Eschwege, E.; Ducimetiere, P.; Paris Prospective, S. Hyperinsulinemia predicts fatal liver cancer but is inversely associated with fatal cancer at some other sites: The Paris Prospective Study. Diabetes Care 2001, 24, 843–849.

7. Tsujimoto, T.; Kajio, H.; Sugiyama, T. Association between hyperinsulinemia and increased risk of cancer death in nonobese and obese people: A population-based observational study. Int. J. Cancer 2017, 141, 102–111.
8. Ma, J.; Giovannucci, E.; Pollak, M.; Leavitt, A.; Tao, Y.; Gaziano, J.M.; Stampfer, M.J. A prospective study of plasma C-peptide and colorectal cancer risk in men. J. Natl. Cancer Inst. 2004, 96, 546–553.
9. Kekalainen, P.; Sarlund, H.; Pyorala, K.; Laakso, M. Hyperinsulinemia cluster predicts the development of type 2 diabetes independently of family history of diabetes. Diabetes Care 1999, 22, 86–92.
10. Mehran, A.E.; Templeman, N.M.; Brigidi, G.S.; Lim, G.E.; Chu, K.Y.; Hu, X.; Botezelli, J.D.; Asadi, A.; Hoffman, B.G.; Kieffer, T.J.; et al. Hyperinsulinemia drives diet-induced obesity independently of brain insulin production. Cell Metab. 2012, 16, 723–737.
11. Sbraccia, P.; D'Adamo, M.; Guglielmi, V. Is type 2 diabetes an adiposity-based metabolic disease? From the origin of insulin resistance to the concept of dysfunctional adipose tissue. Eat Weight Disord. 2021.
12. Shanik, M.H.; Xu, Y.; Skrha, J.; Dankner, R.; Zick, Y.; Roth, J. Insulin resistance and hyperinsulinemia: Is hyperinsulinemia the cart or the horse? Diabetes Care 2008, 31 (Suppl. 2), S262–S268.
13. Corkey, B.E. Banting lecture 2011: Hyperinsulinemia: Cause or consequence? Diabetes 2012, 61, 4–13.
14. Dankner, R.; Chetrit, A.; Shanik, M.H.; Raz, I.; Roth, J. Basal-state hyperinsulinemia in healthy normoglycemic adults is predictive of type 2 diabetes over a 24-year follow-up: A preliminary report. Diabetes Care 2009, 32, 1464–1466.
15. Nolan, C.J.; Ruderman, N.B.; Kahn, S.E.; Pedersen, O.; Prentki, M. Insulin resistance as a physiological defense against metabolic stress: Implications for the management of subsets of type 2 diabetes. Diabetes 2015, 64, 673–686.
16. Schofield, C.J.; Sutherland, C. Disordered insulin secretion in the development of insulin resistance and Type 2 diabetes. Diabet. Med. 2012, 29, 972–979.
17. Aspinwall, C.A.; Lakey, J.R.; Kennedy, R.T. Insulin-stimulated insulin secretion in single pancreatic beta cells. J. Biol. Chem. 1999, 274, 6360–6365.
18. Marfella, R.; D'Amico, M.; Di Filippo, C.; Siniscalchi, M.; Sasso, F.C.; Ferraraccio, F.; Rossi, F.; Paolisso, G. The possible role of the ubiquitin proteasome system in the development of atherosclerosis in diabetes. Cardiovasc. Diabetol. 2007, 6, 35.
19. Crofts, C.; Zinn, C.; Wheldon, M.; Schofield, G. Hyperinsulinemia: A unifying theory of chronic disease. Diabesity 2015, 4, 34–43.
20. Li, C.; Ford, E.S.; McGuire, L.C.; Mokdad, A.H.; Little, R.R.; Reaven, G.M. Trends in hyperinsulinemia among nondiabetic adults in the U.S. Diabetes Care 2006, 29, 2396–2402.
21. Lan-Pidhainy, X.; Wolever, T.M. Are the glycemic and insulinemic index values of carbohydrate foods similar in healthy control, hyperinsulinemic and type 2 diabetic patients? Eur. J. Clin. Nutr. 2011, 65, 727–734.
22. Nilsson, P.; Nilsson, J.A.; Hedblad, B.; Eriksson, K.F.; Berglund, G. Hyperinsulinaemia as long-term predictor of death and ischaemic heart disease in nondiabetic men: The Malmo Preventive Project. J. Intern. Med. 2003, 253, 136–145.
23. Tohidi, M.; Arbab, P.; Ghasemi, A. Assay-dependent variability of serum insulin concentrations: A comparison of eight assays. Scand. J. Clin. Lab. Investig. 2017, 77, 122–129.
24. Porksen, N.; Nyholm, B.; Veldhuis, J.D.; Butler, P.C.; Schmitz, O. In humans at least 75% of insulin secretion arises from punctuated insulin secretory bursts. Am. J. Physiol. 1997, 273, E908–E914.
25. Matthews, D.R. Physiological implications of pulsatile hormone secretion. Ann. N. Y. Acad. Sci. 1991, 618, 28–37.
26. Ward, G.M.; Walters, J.M.; Aitken, P.M.; Best, J.D.; Alford, F.P. Effects of prolonged pulsatile hyperinsulinemia in humans. Enhancement of insulin sensitivity. Diabetes 1990, 39, 501–507.
27. Rizza, R.A.; Mandarino, L.J.; Genest, J.; Baker, B.A.; Gerich, J.E. Production of insulin resistance by hyperinsulinaemia in man. Diabetologia 1985, 28, 70–75.
28. O'Rahilly, S.; Turner, R.C.; Matthews, D.R. Impaired pulsatile secretion of insulin in relatives of patients with non-insulin-dependent diabetes. N. Engl. J. Med. 1988, 318, 1225–1230.
29. Matveyenko, A.V.; Liuwantara, D.; Gurlo, T.; Kirakossian, D.; Dalla Man, C.; Cobelli, C.; White, M.F.; Copps, K.D.; Volpi, E.; Fujita, S.; et al. Pulsatile portal vein insulin delivery enhances hepatic insulin action and signaling. Diabetes 2012, 61, 2269–2279.
30. Meier, J.J.; Veldhuis, J.D.; Butler, P.C. Pulsatile insulin secretion dictates systemic insulin delivery by regulating hepatic insulin extraction in humans. Diabetes 2005, 54, 1649–1656.
31. Gavin, J.R., 3rd; Roth, J.; Neville, D.M., Jr.; de Meyts, P.; Buell, D.N. Insulin-dependent regulation of insulin receptor concentrations: A direct demonstration in cell culture. Proc. Natl. Acad. Sci. USA 1974, 71, 84–88.

32. Le Marchand, Y.; Loten, E.G.; Assimacopoulos-Jeannet, F.; Forgue, M.E.; Freychet, P.; Jeanrenaud, B. Effect of fasting and streptozotocin in the obese-hyperglycemic (ob/ob) mouse. Apparent lack of a direct relationship between insulin binding and insulin effects. Diabetes 1977, 26, 582–590.
33. Zick, Y. Role of Ser/Thr kinases in the uncoupling of insulin signaling. Int. J. Obes. Relat. Metab. Disord. 2003, 27 (Suppl. 3), S56–S60.
34. Zick, Y.; Grunberger, G.; Podskalny, J.M.; Moncada, V.; Taylor, S.I.; Gorden, P.; Roth, J. Insulin stimulates phosphorylation of serine residues in soluble insulin receptors. Biochem. Biophys. Res. Commun. 1983, 116, 1129–1135.
35. Kusari, J.; Kenner, K.A.; Suh, K.I.; Hill, D.E.; Henry, R.R. Skeletal muscle protein tyrosine phosphatase activity and tyrosine phosphatase 1B protein content are associated with insulin action and resistance. J. Clin. Investig. 1994, 93, 1156–1162.
36. Krebs, D.L.; Hilton, D.J. A new role for SOCS in insulin action. Suppressor of cytokine signaling. Sci. STKE 2003, 2003, PE6.
37. Zick, Y. Insulin resistance: A phosphorylation-based uncoupling of insulin signaling. Trends Cell Biol. 2001, 11, 437–441.
38. Ha, J.; Satin, L.S.; Sherman, A.S. A Mathematical Model of the Pathogenesis, Prevention, and Reversal of Type 2 Diabetes. Endocrinology 2016, 157, 624–635.
39. Corkey, B.E. Diabetes: Have we got it all wrong? Insulin hypersecretion and food additives: Cause of obesity and diabetes? Diabetes Care 2012, 35, 2432–2437.
40. Ramlo-Halsted, B.A.; Edelman, S.V. The natural history of type 2 diabetes. Implications for clinical practice. Prim. Care 1999, 26, 771–789.
41. Bergman, R.N.; Piccinini, F.; Kabir, M.; Kolka, C.M.; Ader, M. Hypothesis: Role of Reduced Hepatic Insulin Clearance in the Pathogenesis of Type 2 Diabetes. Diabetes 2019, 68, 1709–1716.
42. Billings, L.K.; Florez, J.C. The genetics of type 2 diabetes: What have we learned from GWAS? Ann. N. Y. Acad. Sci. 2010, 1212, 59–77.
43. Ferrannini, E.; Gastaldelli, A.; Miyazaki, Y.; Matsuda, M.; Mari, A.; DeFronzo, R.A. beta-Cell function in subjects spanning the range from normal glucose tolerance to overt diabetes: A new analysis. J. Clin. Endocrinol. Metab. 2005, 90, 493–500.
44. Pories, W.J.; Dohm, G.L. Diabetes: Have we got it all wrong? Hyperinsulinism as the culprit: Surgery provides the evidence. Diabetes Care 2012, 35, 2438–2442.
45. Lustig, R.H. Which comes first? The obesity or the insulin? The behavior or the biochemistry? J. Pediatrics 2008, 152, 601–602.
46. Hansen, B.C.; Bodkin, N.L. Beta-cell hyperresponsiveness: Earliest event in development of diabetes in monkeys. Am. J. Physiol. 1990, 259, R612–R617.
47. Crofts, C.; Schofield, G.; Zinn, C.; Wheldon, M.; Kraft, J. Identifying hyperinsulinaemia in the absence of impaired glucose tolerance: An examination of the Kraft database. Diabetes Res. Clin. Pract. 2016, 118, 50–57.
48. Weyer, C.; Hanson, R.L.; Tataranni, P.A.; Bogardus, C.; Pratley, R.E. A high fasting plasma insulin concentration predicts type 2 diabetes independent of insulin resistance: Evidence for a pathogenic role of relative hyperinsulinemia. Diabetes 2000, 49, 2094–2101.
49. Ferrannini, E.; Natali, A.; Bell, P.; Cavallo-Perin, P.; Lalic, N.; Mingrone, G. Insulin resistance and hypersecretion in obesity. European Group for the Study of Insulin Resistance (EGIR). J. Clin. Investig. 1997, 100, 1166–1173.
50. Crofts, C.; Zinn, C.; Wheldon, M.; Schofield, G. Hyperinsulinemia: Best management practice. Diabesity 2016, 2, 1–11.
51. Bosello, O.; Zamboni, M.; Armellini, F.; Zocca, I.; Bergamo Andreis, I.A.; Smacchia, C.; Milani, M.P.; Cominacini, L. Modifications of abdominal fat and hepatic insulin clearance during severe caloric restriction. Ann. Nutr. Metab. 1990, 34, 359–365.
52. Bojsen-Moller, K.N.; Dirksen, C.; Jorgensen, N.B.; Jacobsen, S.H.; Serup, A.K.; Albers, P.H.; Hansen, D.L.; Worm, D.; Naver, L.; Kristiansen, V.B.; et al. Early enhancements of hepatic and later of peripheral insulin sensitivity combined with increased postprandial insulin secretion contribute to improved glycemic control after Roux-en-Y gastric bypass. Diabetes 2014, 63, 1725–1737.
53. Bojsen-Moller, K.N.; Lundsgaard, A.M.; Madsbad, S.; Kiens, B.; Holst, J.J. Hepatic Insulin Clearance in Regulation of Systemic Insulin Concentrations-Role of Carbohydrate and Energy Availability. Diabetes 2018, 67, 2129–2136.

54. Tiikkainen, M.; Hakkinen, A.M.; Korsheninnikova, E.; Nyman, T.; Makimattila, S.; Yki-Jarvinen, H. Effects of rosiglitazone and metformin on liver fat content, hepatic insulin resistance, insulin clearance, and gene expression in adipose tissue in patients with type 2 diabetes. Diabetes 2004, 53, 2169–2176.
55. Sutton, E.F.; Beyl, R.; Early, K.S.; Cefalu, W.T.; Ravussin, E.; Peterson, C.M. Early Time-Restricted Feeding Improves Insulin Sensitivity, Blood Pressure, and Oxidative Stress Even without Weight Loss in Men with Prediabetes. Cell Metab. 2018, 27, 1212–1221.e13.
56. Colberg, S.R.; Sigal, R.J.; Fernhall, B.; Regensteiner, J.G.; Blissmer, B.J.; Rubin, R.R.; Chasan-Taber, L.; Albright, A.L.; Braun, B.; American College of Sports, M.; et al. Exercise and type 2 diabetes: The American College of Sports Medicine and the American Diabetes Association: Joint position statement. Diabetes Care 2010, 33, e147–e167.
57. Richard, D.; Labrie, A.; Lupien, D.; Tremblay, A.; LeBlanc, J. Role of exercise-training in the prevention of hyperinsulinemia caused by high energy diet. J. Nutr. 1982, 112, 1756–1762.
58. Teich, T.; Zaharieva, D.P.; Riddell, M.C. Advances in Exercise, Physical Activity, and Diabetes Mellitus. Diabetes Technol. Ther. 2019, 21, S112–S122.
59. Wake, A.D. Antidiabetic Effects of Physical Activity: How It Helps to Control Type 2 Diabetes. Diabetes Metab. Syndr. Obes. 2020, 13, 2909–2923.