Etiopathogenesis of Hypertension with Insulin Resistance in Children

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Contributor: Veronica Maria Tagi , , Francesco Chiarelli

Insulin resistance (IR) is a key component in the etiopathogenesis of hypertension (HS) in patients with diabetes mellitus (DM). The higher risk of developing cardiovascular morbidity in children with a youth-onset Type 2 DM (T2D) is well known. Longitudinal data from the Treatment Options for T2D in Adolescents and Youth (TODAY) study revealed that in a group of 677 participants with a mean age of 14 ± 2 years the cumulative incidence of HS, LDL-C dyslipidemia, and hypertriglyceridemia was 59%, 33%, and 37% respectively and at the end of a mean 10.2 ± 4.5 years follow-up 54% had ≥2 cardiovascular risk factors in addition to T2D.

hypertension insulin resistance diabetes mellitus

1. Introduction

Insulin resistance (IR) is the principal mechanism responsible for the development of HS in patients with DM [1]. In fact, it contributes to an increase blood pressure (BP) in several ways, including the enhanced tissue angiotensin II (AngII) and aldosterone activities [2][3], the increased sympathetic nervous system activity [4], and oxidative stress [5]. Nevertheless, the hypothesis of the “endothelial IR” has been postulated, according to which endotelial disfunction precedes peripheric IR due to the impairment of blood flow in peripheral tissues. This mechanism is mediated by increased oxidative stress, through a protein kinase C β-dependent pathway. In fact, the suppression of reactive oxygen species-dependent pathways in the endothelium has been shown to restore insulin delivery to peripheral organs by preserving nitric oxide (NO) availability [6][7].

The higher risk of developing cardiovascular morbidity in children with a youth-onset Type 2 DM (T2D) is well known. Longitudinal data from the Treatment Options for T2D in Adolescents and Youth (TODAY) study revealed that in a group of 677 participants with a mean age of 14 ± 2 years the cumulative incidence of HS, LDL-C dyslipidemia, and hypertriglyceridemia was 59%, 33%, and 37% respectively and at the end of a mean 10.2 ± 4.5 years follow-up 54% had ≥2 cardiovascular risk factors in addition to T2D. Male sex, non-Hispanic white race/ethnicity, obesity, poor glycemic control, lower insulin sensitivity, and reduced β-cell function were identified as the main risk factors [8].

Agbaje et al. investigated the temporal causal longitudinal associations of carotid-femoral pulse wave velocity (cfPWV), an index of arterial stiffness, with the risk of developing IR, measured with the homeostatic model assessment (HOMA) index, in a group of 3862 followed-up 17.7-year-old participants from the Avon Longitudinal Study of Parents and Children. HOMA index is a paradigm model which allows for determining the IR rate using

only the fasting glucose and insulin values. Levels above 2.9 signal significant insulin resistance. A higher value of HOMAIR corresponds to a more severe IR. The research showed that a higher cfPWV at 17.7 years was associated with higher HOMA index at age 24.5 years, supporting the hypothesis according to which arterial stiffness in adolescence may be a causal risk factor for hyperinsulinemia and IR in young adulthood [9].

Adults with DM are two to four times more likely to die from heart disease than those who do not have DM [10].

The prevalence of HS is higher in patients with DM than in the general population. In fact, it is estimated that about 69.0% have a systolic blood pressure of 140 mmHg or higher or diastolic blood pressure of 90 mmHg or higher or are on prescription medication for their high blood pressure [11]. If HS and DM are both present, the incidences of cardiovascular diseases (CVD) and mortality increase, such as the risks of nephropathy and retinopathy [12][13][14].

Given these premises, specific management of HS in children affected by DM is mandatory. The two most relevant societies that have recently proposed a peculiar treatment and follow-up of children with DM in their guidelines are the European Society of HS [15] and the American Academy of Pediatrics [16].

2. Etiopathogenesis

The association between IR and HS is multifactorial [1].

IR is involved in the development of HS and atherosclerotic cardiovascular disease through three main mechanisms [17]: the basic molecular etiology of IR [18][19][20][21][22][23][24][25][26][27], the compensatory hyperinsulinemia that occurs in response to IR [24][28][29][30][31][32][33][34], and the association between IR and some cardiometabolic abnormalities [28][29][30][35][36].

Insulin acts on its target organs phosphorylating a transmembrane-spanning tyrosine kinase receptor, the insulin receptor (IR). It binds to the α subunit of its receptor activating the tyrosine kinase of the β subunit of the receptor, causing autophosphorylation and phosphorylation of several IR substrates (IRS), such as IRS-1 and IRS-2 [37]. These substrates activate phosphatidylinositol 3-kinase (PI3K), which stimulates Akt, a serine/theronine kinase, which in turn stimulates the glucose uptake through the translocation of GLUT-4, the major glucose transporter to the cell membrane [38]. Akt is also responsible for the activation of nitric oxide synthase, which leads to the production of NO. If this pathway is impaired, NO, which is a potent vasodilator and antiatherogenic agent [28][29], is not produced, favouring vascular resistance, HS and atherogenesis (**Figure 1**).

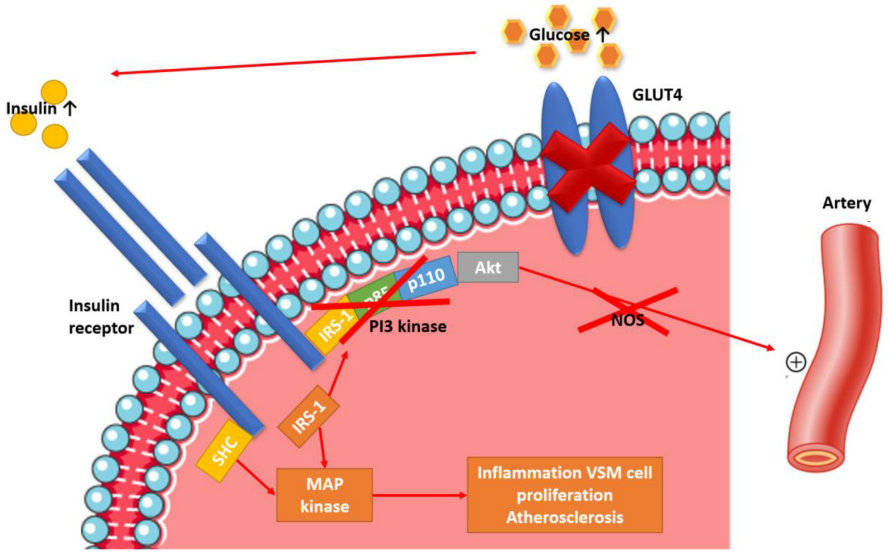

Figure 1. Pathophysiological mechanisms linking IR and hypertension in children with DM. The signaling is impaired at the level of IRS-1, therefore, glucose transport is decreased and nitric oxide synthase activation is impaired, leading to decreased NOS production and therefore vasoconstriction. At the same time, insulin signalling through the MAPK pathway remains normally sensitive to insulin. For this reason, compensatory hyperinsulinemia (secondary to insulin resistance in the IRS-1/PI3K pathway) causes excessive stimulation of the MAPK pathway, which is involved in inflammation, vascular smooth muscle cell proliferation, and atherogenesis. Ab—Abbreviations: NOS—nitric oxide synthase; SHC—Src homology collagen.

One of the mechanisms through which hyperinsulinemia causes an increase of BP is dysregulation of peripheral vascular resistance, stimulating the sympathetic system and therefore causing vasoconstriction [4]; furthermore, hyperinsulinemia contributes to the development of HS-related target organ damage, in particular: impairment of cell membrane ion exchange, enhanced sympathetic nervous and renin-angiotensin systems, suppressed atrial natriuretic peptide activities, sodium retention, and plasma volume expansion lead to chronic kidney disease, left ventricular hypertrophy and carotid atherosclerosis [1].

Moreover, insulin-resistant states, such as T2D, are associated with several cardiometabolic abnormalities factor abnormalities, including elevated PAI-1, increased fibrinogen, and higher platelet stickiness, which are important cardiovascular risk factors [39][40].

Obesity is one of the leading causes of IR [14][28][29], and is strongly associated to atherosclerotic cardiovascular disease [41][42][43].

IR in obese subjects is mainly determined by lipotoxicity: the effect of excessive lipid accumulation which occurs when energy intake exceeds energy consumption [28][29][30]. Elevated free fatty acids in blood promote lipid deposition in tissues, including vessels [44][45][46][47][48][49] and activation of inflammatory pathways [43]. Excessive fat in adipocytes induces enhances the secretion of proinflammatory/prothrombotic cytokines, such as TNFa, PAI-1 and resistin, which promote atherogenesis [50][51][52][53].

References

1. Mancusi, C.; Izzo, R.; di Gioia, G.; Losi, M.A.; Barbato, E.; Morisco, C. Insulin Resistance the Hinge Between hypertension and Type 2 Diabetes. High Blood Press. Cardiovasc. Prev. 2020, 27, 515–526.
2. Steinberg, H.O.; Chaker, H.; Leaming, R.; Johnson, A.; Brechtel, G.; Baron, A.D. Obesity/Insulin resistance is associated with endothelial dysfunction. Implications for the syndrome of insulin resistance. J. Clin. Investig. 1996, 97, 2601–2610.
3. Fukuda, N.; Satoh, C.; Hu, W.Y.; Nakayama, M.; Kishioka, H.; Kanmatsuse, K. Endogenous AngII suppresses insulin signaling in vascular smooth muscle cells from spontaneously hypertensive rats. J. Hypertens. 2001, 19, 1651–1658.
4. Lembo, G.; Napoli, R.; Capaldo, B.; Rendina, V.; Iaccarino, G.; Volpe, M.; Trimarco, B.; Sacca, L. Abnormal sympathetic overactivity evoked by insulin in the skeletal muscle of patients with essential hypertension. J. Clin. Investig. 1992, 90, 24–29.
5. Sowers, J.R. hypertension, AngII, and oxidative stress. N. Engl. J. Med. 2002, 346, 1999–2001.
6. Tabit, C.E.; Chung, W.B.; Hamburg, N.M.; Vita, J.A. Endothelial dysfunction in diabetes mellitus: Molecular mechanisms and clinical implications. Rev. Endocr. Metab. Disord. 2010, 11, 61–74.
7. Tabit, C.E.; Shenouda, S.M.; Holbrook, M.; Fetterman, J.L.; Kiani, S.; Frame, A.A.; Kluge, M.A.; Held, A.; Dohadwala, M.M.; Gokce, N.; et al. Protein kinase C-β contributes to impainsulin resistanceed endothelial insulin signaling in humans with diabetes mellitus. Circulation 2013, 127, 86–95.
8. TODAY Study, Group; Shah, R.D.; Braffett, B.H.; Tryggestad, J.B.; Hughan, K.S.; Dhaliwal, R.; Nadeau, K.J.; Levitt Katz, L.E.; Gidding, S.S. Cardiovascular risk factor progression in adolescents and young adults with youth-onset type 2 diabetes. J. Diabetes Complicat. 2022, 36, 108123.
9. Agbaje, A.O.; Barker, A.R.; Mitchell, G.F.; Tuomainen, T.P. Effect of Arterial Stiffness and Carotid Intima-Media Thickness Progression on the Risk of Dysglycemia, Insulin Resistance, and Dyslipidemia: A Temporal Causal Longitudinal Study. Hypertension 2022, 79, 667–678.
10. Passarella, P.; Kiseleva, T.A.; Valeeva, F.V.; Gosmanov, A.R. Hypertension Management in DIABETES: 2018 Update. Diabetes Spectr. 2018, 31, 218–224.
11. Centers for Disease Control and Prevention. National Diabetes Statistics Report website. Available online: https://www.cdc.gov/diabetes/data/statistics-report/index.html. (accessed on 21 May 2022).

12. Adler, A.I.; Stratton, I.M.; Neil, H.A.W.; Yudkin, J.S.; Matthews, D.R.; Cull, C.A.; Wright, A.D.; Turner, R.C.; Holman, R.R. Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): Prospective observational study. BMJ 2000, 321, 412–419.
13. Gosmanov, A.R.; Lu, J.L.; Sumida, K.; Potukuchi, P.K.; Rhee, C.M.; Kalantar-Zadeh, K.; Molnar, M.Z.; Kovesdy, C.P. Synergistic association of combined glycemic and blood pressure level with risk of complications in US veterans with diabetes. J. Hypertens. 2016, 34, 907–913.
14. Stamler, J.; Vaccaro, O.; Neaton, J.D.; Wentworth, D. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. Diabetes Care 1993, 16, 434–444.
15. Lurbe, E.; Agabiti-Rosei, E.; Cruickshank, J.K.; Dominiczak, A.; Erdine, S.; Hinsulin, A.; Invitti, C.; Litwin, M.; Mancia, G.; Pall, D.; et al. 2016 European Society of Hypertension guidelines for the management of high blood pressure in children and adolescents. J. Hypertens. 2016, 34, 1887–1920.
16. Flynn, J.T.; Kaelber, D.C.; Baker-Smith, C.M.; Blowey, D.; Carroll, A.E.; Daniels, S.R.; de Ferranti, S.D.; Dionne, J.M.; Falkner, B.; Flinn, S.K.; et al. Subcommittee on Screening and Management of High Blood Pressure in Children. Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents. Pediatrics 2017, 140, e20171904.
17. Di Pino, A.; DeFronzo, R.A. Insulin Resistance and Atherosclerosis: Implications for Insulin-Sensitizing Agents. Endocr. Rev. 2019, 40, 1447–1467.
18. Petersen, M.C.; Shulman, G.I. Mechanisms of insulin action and insulin resistance. Physiol. Rev. 2018, 98, 2133–2223.
19. Bajaj, M.; Defronzo, R.A. Metabolic and molecular basis of insulin resistance. J. Nucl. Cardiol. 2003, 10, 311–323.
20. Rask-Madsen, C.; Li, Q.; Freund, B.; Feather, D.; Abramov, R.; Wu, I.H.; Chen, K.; Yamamoto-Hinsulin, J.; Goldenbogen, J.; Sotinsulin, K.B.; et al. Loss of insulin signaling in vascular endothelial cells accelerates atherosclerosis in apolipoprotein E null mice. Cell Metab. 2010, 11, 379–389.
21. Jiang, Z.Y.; Lin, Y.W.; Clemont, A.; Feener, E.P.; Hein, K.D.; Igarashi, M.; Yamauchi, T.; White, M.F.; King, G.L. Characterization of selective resistance to insulin signaling in th.he vasculature of obese Zucker (fa/fa) rats. J. Clin. Investig. 1999, 104, 447–457.
22. Cusi, K.; Maezono, K.; Osman, A.; Pendergrass, M.; Patti, M.E.; Pratipanawatr, T.; DeFronzo, R.A.; Kahn, C.R.; Mandarino, L.J. Insulin resistance differentially affects the PI 3-kinase- and MAP kinase-mediated signaling in human muscle. J. Clin. Investig. 2000, 105, 311–320.

23. Sasaoka, T.; Rose, D.W.; Jhun, B.H.; Saltiel, A.R.; Draznin, B.; Olefsky, J.M. Evidence for a functional role of Shc proteins in mitogenic signaling induced by insulin, insulin-like growth factor-1, and epidermal growth factor. J. Biol. Chem. 1994, 269, 13689–13694.
24. Hypertensionueh, W.A.; Law, R.E. Insulin signaling in the arterial wall. Am. J. Cardiol. 1999, 84, 21J–24J.
25. Wang, C.C.; Goalstone, M.L.; Draznin, B. Molecular mechanisms of insulin resistance that impact cardiovascular biology. Diabetes 2004, 53, 2735–2740.
26. Draznin, B. Molecular mechanisms of insulin resistance: Serine phosphorylation of insulin receptor substrate-1 and increased expression of p85a: The two sides of a coin. Diabetes 2006, 55, 2392–2397.
27. King, G.L.; Park, K.; Li, Q. Selective insulin resistance and the development of cardiovascular diseases in diabetes: The 2015 Edwin Bierman Award Lecture. Diabetes 2016, 65, 1462–1471.
28. DeFronzo, R.A. From the triumvinsulin resistanceate to the ominous octet: A new paradigm for the treatment of type 2 diabetes mellitus. Diabetes 2009, 58, 773–795.
29. DeFronzo, R.A. Insulin resistance, lipotoxicity, type 2 diabetes and atherosclerosis: The missing links. The Claude Bernard Lecture 2009. Diabetologia 2010, 53, 1270–1287.
30. Reaven, G.M. Banting lecture 1988. Role of insulin resistance in human disease. Diabetes 1988, 37, 1595–1607.
31. Sasaoka, T.; Ishiki, M.; Sawa, T.; Ishihara, H.; Takata, Y.; Imamura, T.; Usui, I.; Olefsky, J.M.; Kobayashi, M. Comparison of the insulin and insulin-like growth factor 1 mitogenic intracellular signaling pathways. Endocrinology 1996, 137, 4427–4434.
32. Pfeifle, B.; Ditschuneit, H. Effect of insulin on growth of cultured human arterial smooth muscle cells. Diabetologia 1981, 20, 155–158.
33. Leitner, J.W.; Kline, T.; Carel, K.; Goalstone, M.; Draznin, B. Hyperinsulinemia potentiates activation of p21Ras by growth factors. Endocrinology 1997, 138, 2211–2214.
34. Ferrannini, E.; Natali, A.; Muscelli, E.; Nilsson, P.M.; Golay, A.; Laasko, M.; Beck-Mielsen, H.; Mari, H. RISC Investigators. Natural history and physiological determinants.of changes in glucose tolerance in a non-diabetic population: The RISC study. Diabetologia 2011, 54, 1507–1516.
35. DeFronzo, R.A.; Ferrannini, E. Insulin Resistance. A multifaceted syndrome responsible for NID diabetes, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. Diabetes Care 1991, 14, 173–194.
36. Ferrannini, E.; Balkau, B.; Coppack, S.W.; Dekker, J.M.; Mari, A.; Nolan, J.; Walker, M.; Natali, A.; Beck-Nielsen, H.; RISC Investigators. Insulin resistance, insulin response, and obesity as indicators of metabolic risk. J. Clin. Endocrinol. Metab. 2007, 92, 2885–2892.

37. Lee, J.; Pilch, P.F. The insulin receptor: Structure, function, and signaling. Am. J. Physiol. 1994, 266, C319–C334.

38. Cong, L.N.; Chen, H.; Li, Y.; Zhou, L.; McGibbon, M.A.; Taylor, S.I.; Quon, M.J. Physiological role of akt in insulin-stimulated translocation of glut4 in transfected rat adipose cells. Mol. Endocrinol. 1997, 11, 1881–1890.

39. Stegenga, M.E.; van der Crabben, S.N.; Levi, M.; de Vos, A.F.; Tanck, M.W.; Sauerwein, H.P.; van der Poll, T. Hyperglycemia stimulates coagulation, whereas hyperinsulinemia impainsulin resistances fibrinolysis in healthy humans. Diabetes 2006, 55, 1807–1812.

40. Dunn, E.J.; Philippou, H.; Ariens, R.A.; Grant, P.J. Molecular mechanisms involved in the resistance of fibrin to clot lysis by plasmin in subjects with type 2 diabetes mellitus. Diabetologia 2006, 49, 1071–1080.

41. Holman, R.R.; Thorne, K.I.; Farmer, A.J.; Davies, M.J.; Keenan, J.F.; Paul, S.; Levy, J.C. Addition of biphasic, prandial, or basal insulin to oral therapy in type 2 diabetes. N. Engl. J. Med. 2007, 357, 1716–1730.75.

42. Purnell, J.Q.; Dev, R.K.; Steffes, M.W.; Cleary, P.A.; Palmer, J.P.; Hinsulin, I.B.; Hokanson, J.E.; Brunzell, J.D. Relationship of family history of type 2 diabetes, hypoglycemia, and autoantibodies to weight gain and lipids with intensive and conventional therapy in the Diabetes Control and Complications Trial. Diabetes 2003, 52, 2623–2629.

43. Smith, U. Abdominal obesity: A marker of ectopic fat accumulation. J Clin Investig. 2015, 125, 1790–1792.

44. Bajaj, M.; Baig, R.; Suraamornkul, S.; Hardies, L.J.; Coletta, D.K.; Cline, G.W.; Monroy, A.; Koul, S.; Sriwijitkamol, A.; Musi, N.; et al. Effects of pioglitazone on intramyocellular fat metabolism in patients with type 2 diabetes mellitus. J. Clin. Endocrinol. Metab. 2010, 95, 1916–1923.

45. Bays, H.; Mandarino, L.; DeFronzo, R.A. Role o.of the adipocyte, free fatty acids, and ectopic fat in pathogenesis of type 2 diabetes mellitus: Peroxisomal proliferator-activated receptor agonists provide a rational therapeutic approach. J. Clin. Endocrinol. Metab. 2004, 89, 463–478.

46. Bajaj, M.; Suraamornkul, S.; Romanelli, A.; Cline, G.W.; Mandarino, L.J.; Shulman, G.I.; DeFronzo, R.A. Effect of a sustained reduction in plasma free fatty acid concentration on intramuscular long-chain fatty acyl-CoAs and insulin action in type 2 diabetic patients. Diabetes 2005, 54, 3148–3153.

47. Inoguchi, T.; Li, P.; Umeda, F.; Yu, H.Y.; Kakimoto, M.; Imamura, M.; Aoki, T.; Etoh, T.; Hashimoto, T.; Naruse, M.; et al. High glucose level and free fatty acid stimulate reactive oxygen species production through protein kinase C—Dependent activation of NAD(P)H oxidase in cultured vascular cells. Diabetes 2000, 49, 1939–1945.

48. Mathew, M.; Tay, E.; Cusi, K. Elevated plasma free fatty acids increase cardiovascular risk by inducing plasma biomarkers of endothelial activation, myeloperoxidase and PAI-1 in healthy subjects. Cardiovasc. Diabetol. 2010, 9, 9.
49. Wende, A.R.; Symons, J.D.; Abel, E.D. Mechanisms of lipotoxicity in the cardiovascular system. Curr. Hypertens. Rep. 2012, 14, 517–531.
50. Richardson, D.K.; Kashyap, S.; Bajaj, M.; Cusi, K.; Mandarino, S.J.; Finlayson, J.; DeFronzo, R.A.; Jenkinson, C.P.; Mandarino, L.J. Lipid infusion decreases the expression of nuclear encoded mitochondrial genes and increases the expression of extracellular matrix genes in human skeletal muscle. J. Biol. Chem. 2005, 280, 10290–10297.
51. Dresner, A.; Laurent, D.; Marcucci, M.; Grifffin, M.E.; Dufour, S.; Cline, G.W.; Slezak, L.A.; Andersen, D.K.; Hundal, R.S.; Rothman, D.L.; et al. Effects of free fatty acids on glucose transport and insulin resistance-1-associated phosphatidylinositol 3-kinase activity. J. Clin. Investig. 1999, 103, 253–259.
52. Belfort, R.; Mandarino, L.; Kashyap, S.; Winsulin, K.; Pratipanawatr, T.; Berria, R.; DeFronzo, R.A.; Cusi, K. Dose-response effect of elevated plasma free fatty acid on insulin signaling. Diabetes 2005, 54, 1640–1648.
53. Kim, J.K.; Fillmore, J.J.; Chen, Y.; Yu, C.; Moore, I.K.; Pypaert, M.; Lutz, E.P.; Kako, Y.; Velez-Carrasco, W.; Goldberg, I.J.; et al. Tissue-specific overexpression of lipoprotein lipase causes tissue-specific insulin resistance. Proc. Natl. Acad. Sci. USA 2001, 98, 7522–7527.