NO (Nitric Oxide) to Type 2 Diabetes Induced Endothelial Dysfunction: Crosstalk with ET-1 (Endothelin-1)

Omanwar Swati*, Gupta Charu, Dhyani Neha and Saidullah Bano

School of Sciences, Indira Gandhi National Open University, India

Submission: July 24, 2017; Published: September 27, 2017

*Corresponding author: Omanwar Swati, School of Sciences, Indira Gandhi National Open University, India, Tel: 91-01129572818; Email: swatiomanwar@gmail.com

Abstract

Vascular endothelium is a fundamental part of the blood vessel and sustains homeostasis of the circulatory system and normal arterial function. Experimental and clinical studies suggest that insulin resistance in diabetes is associated with functional disorder of endothelium and higher risk of cardiovascular disease (CVD). Insulin resistance causes reduction in nitric oxide (NO) bioavailability and increase in endothelin-1 (ET-1) secretion which plays a vital part in the development of endothelial dysfunction. ET-1 causes a decrease in adiponectin secretion (hypo adiponectinaemia which is correlated with diabetes/impaired insulin signaling) which has also been identified as an independent risk factor for CVD. This mini review investigates and appraises the impact of insulin resistant Type 2 diabetes (T2DM) on endothelium derived vasodilator, NO, and vasoconstrictor ET-1 highlighting crosstalk between them.

Keywords: Diabetes; Cardiovascular disease; Endothelium; Insulin; NO; ET-1; Oxidative stress; Adiponectin

Mini Review

Cardiovascular diseases (CVD) are one of the major causes for the most non communicable disease (NCD) related deaths worldwide (17.5 million deaths annually). Diabetes is the third highest contributor to NCD deaths (1.5 million) trailing behind cancers and respiratory diseases [1].

A key feature of CVDs is endothelial dysfunction characterized by a reduction in bioavailability of the signaling radical NO. T2DM is associated with systemic insulin resistance, which promotes hyperglycemia and dyslipidemia [2] and leads to reduced bioavailability of NO, indicative of a critical role for insulin in regulating NO bioavailability [3-5].

Insulin is the most effective anabolic peptide hormone which helps in the synthesis and storage of carbohydrates, lipids and proteins and is made by the β cells, of the islets of Langerhans in the pancreas [6]. As a major regulator of vascular homeostasis, insulin helps the endothelium in maintaining the balance between vasodilation and vasoconstriction, by stimulating production of both NO and ET-1. Impairment in the functioning of insulin (T2DM) or production of insulin (type I diabetes) or both disturbs this tightly regulated equilibrium between NO and ET-1 leading to endothelial dysfunction, decreased blood flow and ultimately to CVDs [7]. Decreased blood flow due to endothelial dysfunction further aggravates diabetes as it causes reduced delivery of blood to pancreas, resulting in further decrease in insulin secretion. A vicious cycle between insulin resistance and endothelial dysfunction develops which is amplified synergistically. A recent study has demonstrated that ET-1 also has the ability to regulate adiponectin secretion [8]. Adiponectin is an insulin sensitizing hormone which is a potent vasodilator and antioxidant and, its vasodilatory effect is also mediated via a NO-dependent mechanism [9-11]. This mechanism is disrupted in T2DM, a phenomenon potentiated by excessive accumulation of reactive oxygen species (ROS). Though multiple independent and interdependent factors such as hyperglycemia, dyslipidemia, inflammatory cytokines hypo adiponectinemia, oxidative stress contribute in the fierce synergy linking insulin resistance and endothelial dysfunction, this mini review focuses only on the vasoactive role of insulin in T2DM on endothelial function and vice versa due to the interplay of NO and ET-1.

NO and ET-1 cross talk in T2DM

The vascular endothelium has fundamental control on the maintenance and modulation of vascular tone. In the
healthy state, endothelium continually produces NO and other vasodilator molecules (prostacyclin, endothelium-derived hyperpolarizing factor (EDHF), bradykinin, adrenomedullin, C-natriuretic peptide), thereby promoting a relaxed vascular state; however, they also concurrently form and release ET-1 and other constricting factors, (angiotensin-II, thromboxane A2, prostaglandins, hydrogen peroxide (H2O2) and free radicals) which help to modulate the tone of the vascular bed [12]. The L-arginine-NO pathway is thought to be the most important enzymatic vasodilator source and ET-1 the most potent vasoconstrictor. The basal and stimulated production of NO inhibits the synthesis of ET-1 by endothelial cells. Thus, the direct vasoconstrictor action of ET-1 is modulated by the stimulation of the release of NO. It appears that a delicate balance exists between ET-1 and NO released. When there is an increase in NO release, enhanced endothelial function is observed. In pathological conditions like T2DM the balance between NO and ET-1 is disturbed by generation of free radicals (due to dyslipidemia, hyperglycemia, hypoadiponectinemia ) which causes a decrease in bioavailability NO, increased ET-1 production directly or indirectly by modulation of insulin signaling. Several groups have proposed that the hemodynamic effects of insulin are regulated by the balance between the vasodilator and vasoconstrictor effects of NO and ET-1, respectively [13-15]. In addition, as the actions of ET-1 and NO are mutually antagonistic, any imbalance, is amplified leading to endothelial dysfunction and subsequently CVDs. NO and ET-1 have emerged as central pathophysiological players in endothelial dysfunction [16,17].

Insulin exerts its metabolic and vasoactive actions via the phosphatidylinositol 3-kinase (PI-3 kinase) and mitogen-activated protein kinase (MAPK) signaling pathways. Insulin binds and activates the insulin receptor tyrosine kinase (IR) resulting in phosphorylation of insulin receptor substrates (IRS) and activation of PI-3 kinase and protein kinase B (PKB or Akt) [18]. This causes the translocation of glucose transporter 4 and activation of PI-3 kinase and protein kinase B (PKB or Akt). In T2DM, compensatory hyperinsulinemia results in endothelium dysfunction due to decreased NO bioavailability [16,17]. The imbalance between PI3K/Akt/eNOS/NO and MAPK/ET-1 vascular actions of insulin attributes to endothelial dysfunction and subsequently to CVD [28,29]. Apart from hyperinsulinemia, T2DM is accompanied by dyslipidemia, hyperglycemia, hypoadiponectinemia and inflammatory cytokines which contribute in the generation of oxidative stress. One of the other mechanism which links ET-1 to NO in T2DM may be via formation of ROS, which results in decreased bioactivity of NO by virtue of formation of peroxynitrite. Recent data demonstrate that ET-1 mediates superoxide production along with vasoconstriction [30]. Further, increase in ET-1 in T2DM causes downregulation in the expression of eNOS [31] and adiponectin deficiency [8]. Adiponectin, is down-regulated in obesity and its related pathologies [32]. There is some evidence suggesting involvement of PI3K in adiponectin-induced production of endothelial NO, possibly via activation of AMP kinase [33-35]. Adiponectin improves the redox state in human vessels by restoring eNOS coupling [36]. In an ex vivo study on aorta of T2DM mice an increase NO bioavailability was observed after treatment with adiponectin indicating that adiponectin decreases superoxide production [37]. The adiponectin has the ability to oppose ET-1-mediated vasoconstriction which may be an important aspect of its insulin-sensitizing actions [38].

Mostly endothelial dysfunction often refers to a situation of reduced bioavailability and consequently impaired vasodilator effect of endothelium-derived relaxing factors of NO, along with an additional important alteration in endothelial dysfunction is an increased production and biological activity ET-1. Insulin produces NO through PI3/Akt pathway and ET-1 by MAPK pathway. In T2DM, compensatory hyperinsulinemia results in endothelium dysfunction due to decreased NO bioavailability (disruptive PI3/Akt pathway, oxidative stress and decrease in adiponectin) and increase in ET-1 (activated MAPK pathway, oxidative stress). Progressive deregulation of the relationship between ET-1 and NO due to insulin resistance, adiponectin deficiency and oxidative stress, may be one of the major contributory factor for endothelial dysfunction observed in T2DM.

Reference

1. World Health Organization. Non communicable diseases Fact Sheet. January 2015.
2. Eckel RH, Wass m M, Chait A, Sobel B, Barrett E, et al. (2002) Prevention conference VI: Diabetes and cardiovascular disease: writing Group II: pathogenesis of atherosclerosis in diabetes. Circulation 105(18): e138-e143.
3. Wheatcroft SB, Shah AM, Li JM, Duncan E, Norohna BT, et al. (2004) Preserved gluconeogenesis but attenuation of the vascular actions of insulin in mice heterozygous for knockout of the insulin receptor. Diabetes 53(10): 2645-2652.
4. Kahn MB, Yuldasheva NY, Cubbon RM, Smith J, Rashid ST, et al. (2011) Insulin resistance impairs circulating angiogenic progenitor cell function and delays endothelial regeneration. Diabetes 60(4): 1295-1303.
5. Duncan ER, Crose WA, Walker S, Anilkumar N, Poston L, et al. (2008) Effect of endothelium-specific insulin resistance on endothelial function in vivo. Diabetes 57(12): 3307-3314.

6. Saltiel AR, Kahn CR (2001) Insulin signalling and the regulation of glucose and lipid metabolism. Nature 414: 799-806.

7. Vanhoutte PM, Shimokawa H, Tang EH, Feletou M (2009) Endothelial dysfunction and vascular disease. Acta Physiol (Oxf) 196(2): 193-222.

8. Clarke KJ, Zhong Q, Schwartz DD, Coleman ES, Kemppainen RJ, et al. (2003) Regulation of adiponectin secretion by endothelin-1. Biochem Biophys Res Commun 312(4):945-949.

9. Cheng KK, Lam KS, Wang Y, Huang Y, Carling D, et al. (2007) Adiponectin-induced endothelial nitric oxide synthase activation and nitric oxide production are mediated by APPL1 in endothelial cells. Diabetes 56(5): 1387-1394.

10. Schmid PM, Resch M, Steegen A, Fredersdorf HS, Stoelcker B, et al. (2011) Globular and Full-Length Adiponectin Induce NO-Dependent Vasodilation in Resistance Arteries of Zucker Lean but Not Zucker Diabetic Fatty Rats. Am J Hypertens 24(3): 270-277.

11. Xi W, Satoh H, Kase H, Suzuki K, Yoshiyuki H (2005) Stimulated HSP90 binding to eNOS and activation of the PI3-Akt pathway contribute to globular adiponectin-induced NO production: vasorelaxation in response to globular adiponectin. Biochem Biophys Res Commun 321(1): 200-205.

12. McGuire JJ, Ding H, Triggle CR (2001) Endothelium-derived relaxing factors: a focus on endothelium-derived hyperpolarizing factor(s). Can J Physiol Pharmacol 79(6): 443-470.

13. Cardillo C, Nambi SS, Kicoyne CM, Choucair WK, Katz A, et al. (1999) Insulin stimulates both endothelin and nitric oxide activity in the human forearm. Circulation 100(8): 820-825.

14. Eringa EC, Stehouwer CDA, Merlijn T, Westerhoff N, Sipkema P (2002) Physiological concentrations of insulin induce endothelin-mediated vasoconstriction during inhibition of NOS or PI3-kinase in skeletal muscle arteries. Cardiovasc Res 56(3): 464-471.

15. Verma S, Yao L, Stewart DJ, Dumont AS, Anderson TJ, et al. (2001) Endothelin antagonist uncovers insulin-mediated vasorelaxation in vitro and in vivo. Hypertension 37(2): 320-333.

16. Barton M, Yanagisawa M (2008) Endothelin 20 years from discovery to therapy. Can J Physiol Pharmacol 86(8): 485-498.

17. Yanagisawa M, Kurihara H, Kimura S, Tomobe Y, Kobayashi M, et al. (1988) A novel potent vasoconstrictor peptide produced by vascular endothelial cells. Nature 332(6163): pp. 411-415.

18. Taniguchi CM, Emanuelli B, Kahn CR (2006) Critical nodes in signalling pathways: insights into insulin action. Nat Rev Mol Cell Biol 7(2): 85-96.

19. Moniokski M, Reddick RL (1982) Vascular smooth muscle. A unifying theory. Am J Pathol 107(3): 183-190.

20. Barton M, Yanagisawa M (2008) Endothelin 20 years from discovery to therapy. Can J Physiol Pharmacol 86(8): 485-498.

21. Chiu CC, Chang TY, Chang CL, Huang SW, Ho LT (2007) Endothelin-1 regulates adiponectin gene expression and secretion in 3T3-L1 adipocytes via distinct signaling pathways. Endocrinology 148(4): 1835-1842.

22. Ferric C, Carlomagno A, Coassin S (1995) Circulating endothelin-1 levels increase during euglycemic hyperinsulinemic clamp in lean NIDDM men. Diabetes Care 18:226-233.

23. Munleppa R, Montagnani M, Koh KK (2007) Cardiovascular actions of insulin. Endocr Rev; 28(5): 463–491.

24. Potenza MA, Marasciulo FL, Chiappa DM, et al. (2005) Insulin resistance in spontaneously hypertensive rats is associated with endothelial dysfunction characterized by imbalance between NO and ET-1 production. Am J Physiol Heart Circ Physiol 289: H813-822.

25. Formoso G, Chen H, Kim JA, et al. (2006) Dehydroepiandrosterone mimics acute actions of insulin to stimulate production of both nitric oxide and endothelin 1 via distinct phosphatidylinositol-3-kinase- and mitogen-activated protein kinase-dependent pathways in vascular endothelium. Mol Endocrinol 20(11):1153-1163.

26. Potenza MA, Marasciulo FL, Tarquinio M, et al. (2006) Treatment of spontaneously hypertensive rats with rosiglitazone and/or enalapril restores balance between vasoconstriction and vessel-protective actions of insulin with simultaneous improvement in hypertension and insulin resistance. Diabetes 55: 3594-3603.

27. Sarsafizad PA, Bakris GL (2007) Review: Insulin and endothelin: an interplay contributing to hypertension development? J Clin Endocrinol Metab 92(2):379-85. Epub 2006 Nov 21. Review. PubMed PMID: 17118997.

28. Clarke KJ, Zhong Q, Schwartz DD, et al. (2003) Regulation of adiponectin secretion by endothelin-1. BiochemBiophys Res Commun 312(4): 945-949. PubMed PMID: 14651962.

29. Juan CC, Chang TY, Chang CL, et al. (2007) Endothelin-1 regulates adiponectin gene expression and secretion in 3T3-L1 adipocytes via distinct signaling pathways. Endocrinology 148(4): 1835-1842. Epub 2006 Dec 28. PubMed PMID: 17194742.

30. Loomis ED, Sullivan JC, Osmond DA, et al. (2005) Endothelin mediates superoxide production and vasoconstriction through activation of NADPH oxidase and uncoupled nitric-oxide synthase in the rat aorta. J Pharmacol Exp Ther 315: 1058-1064.

31. Ramzy D, Rao V, Tumirati LC, et al. (2006) Elevated endothelin-1 levels impair nitric oxide homeostasis through a PKC-dependent pathway. Circulation 114: 1319-1326.

32. Hideaki K, Naoto K, Munehide M et al. (2010) Role of Reactive Oxygen Species in the Progression of Type 2 Diabetes and Atherosclerosis Mediators Inflamm:453892.

33. Zhu W, Cheng KK, Vanhoutte PM, et al. (2008) Vascular effects of adiponectin: molecular mechanisms and potential therapeutic intervention A Clin Sci (Lond) 114(5): 361-74.

34. McIntosh H, Montagnani M, Funahashi T, et al. (2003) Adiponectin stimulates production of nitric oxide in vascular endothelial cells. Biochem Biophys Res Commun 312(4): 945-949. PubMed PMID: 14651962.

35. Juan CC, Chang TY, Chang CL, et al. (2007) Endothelin-1 regulates adiponectin gene expression and secretion in 3T3-L1 adipocytes via distinct signaling pathways. Endocrinology 148(4): 1835-1842. Epub 2006 Dec 28. PubMed PMID: 17194742.

36. Xi W, Satoh H, Kase H, et al. (2005) Stimulated HSP90 binding to eNOS and activation of the PI3-Akt pathway contribute to globular adiponectin-induced NO production: vasorelaxation in response to globular adiponectin. Biochem Biophys Res Commun 312(4): 945-949.

37. Taniguchi CM, Emanuelli B, Kahn CR (2006) Critical nodes in signalling pathways: insights into insulin action. Nat Rev Mol Cell Biol 7(2): 85-86.

38. Montagnani M, Chen H, Barr VA, Quon M (2001) Insulin-stimulated activation of enos is independent of calcium but requires phosphorylation by akt at ser1179. J Biol Chem 276(12): 30392-30398.

39. Zeng G, Quon M (1996) Insulin-stimulated production of nitric oxide is inhibited by wortmannin. Direct measurement in vascular endothelial cells. Journal of Clinical Investigation 98(4): 894-898.

40. Clarke KJ, Zhong Q, Schwartz DD, Coleman ES, Kemppainen RJ, et al. (2003) Regulation of adiponectin secretion by endothelin-1. Biochem Biophys Res Commun 312(4): 945-9. PubMed PMID: 14651962.

41. Juan CC, Chang TY, Chang CL, Huang SW, Ho LT (2007) Endothelin-1 regulates adiponectin gene expression and secretion in 3T3-L1 adipocytes via distinct signaling pathways. Endocrinology 148(4): 1835-1842.
