The Role of Vistafin in Diabetes-Induced Impairment of Endothelial Repair System

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Received Date: October 31, 2016; Accepted Date: February 02, 2017; Published Date: February 07, 2017

Citation: Berezin AE. The Role of Vistafin in Diabetes-Induced Impairment of Endothelial Repair System. Transl Biomed. 2017, 8:1.

Abstract

Type 2 diabetes mellitus (T2DM) is considered a leading factor of cardiovascular (CV) events in general population. Impairment of endogenous endothelial repair system plays a pivotal role in T2DM-induced microangiopathy and macroangiopathy and, however, may contribute in CV risk and outcomes. Recent studies have shown that the nicotinamide phosphoribosyl transferase (NAMPT) currently known as visfatin has reported an integral adipocytokine with proinflammatory and immunomodulating properties. It is suggested that visfatin/NAMPT may act as multifunctional agent with undefined effect on several targets especially endothelial cells and progenitor cells depending of metabolic status of the patients. The short commentary is discussed a possible role of visfatin/NAMPT as a biomarker of nature evolution of T2DM and as a target for therapeutic strategy aimed to improve endothelial function in T2DM patients in future.

Keywords: Diabetes mellitus; Vasculopathy; Endothelial dysfunction; Endothelial repair system; Progenitor cells

Introduction

Diabetes mellitus (DM) remains a global health problem and social burden worldwide [1]. Recent studies have shown that diabetes especially type 2 (T2DM) exhibited closely association with cardiovascular (CV) mortality and morbidity [2,3]. In fact, glucose toxicity and lipid toxicity, as the most important components of DM pathogenesis, contribute in over production of various spectrums of cytokines, which may be involved in the progress of disease via regulating apoptosis, differentiation, and inflammation [4,5]. Moreover, inflammatory cytokines are involved in the pathogenesis of DM-induced microangiopathy, macroangiopathy, and accelerating atherosclerosis [6,7]. Amongst of these cytokines the nicotinamide phosphoribosyl transferase (NAMPT), currently known as visfatin, has qualified an integral adipocytokine with proinflammatory and immunomodulating properties [8].

Vistafin/NAMPT is a 52 kDa protein, which was first found out in 1994 and then the abundant diverse functions of one in the various physiological processes and human disease were evaluated [9]. Indeed, visfatin/NAMPT has been existing in two forms (intracellular and extracellular) acts as a powerful growth factor, inflammatory cytokine, enzyme/coenzyme in metabolic processes, as well as an insulin-mimetic agent [10]. The intracellular form of Vistafin is highly expressed in adipose tissue, liver, and kidney, whereas the free circulating extracellular form is mainly secreted in serum from mononuclears, hepatocytes, cardiomyocytes and completely differentiated adipocytes [8,11].

Recent preclinical studies have shown that Vistafin induces cholesterol accumulation in macrophages through up-regulation of scavenger receptor-A and CD36 that subsequently leads to transformation of them into foam cells [12,13]. Observational and clinical investigations have confirmed that Vistafin could be a marker of atherosclerosis, insulin resistance, systemic inflammatory response, infectious processes, and adipocytokines’ dysfunction [9,11,14,15]. These effects of Vistafin are predominantly resulting in an ability to regulate the activity of NAD-dependent protein deacetylase Sirtuin-2, which is a key factor in an induction of the inflammatory cytokines (interleukin [IL]-1β, IL-6, tumor necrosis factor alpha) and growth factors (transforming growth factor β1) production [16]. Nevertheless, vistafin is a modulator of apoptosis, oxidative stress and chemotaxis of activated mononuclears [10,17]. In contrast, there is a large body of evidence regarding that the vistafin might exhibit a protective effect against high glucose level in endothelial cells, ability to inducing cell proliferation, and attenuating angiogenesis and endothelial cell reparation [9,11]. Thus, Vistafin acts as multifunctional metabolic agent with regulatory effect on several targets especially endothelial cells and progenitor cells.

Altered function and decreased number of circulating endothelial progenitor cells (EPCs) in T2DM have well established and it is now widely discussed a key factor contributing in impaired endothelial reparation and CV event manifestation [18]. Indeed, EPCs have a protective impact on the endothelium and mediate the reparation of the vasculature [19]. Interestingly, reduced number and weak functionality of circulating EPCs known as “impaired” phenotype have shown a close association with both
traditional including T2DM and non-traditional (insulin resistance, adipocyte dysfunction) CV risk factors as well as Framingham risk factor score [6]. Most importantly, the impaired phenotype of EPCs is a key feature of DM-induced vasculopathy, although at the early stage of DM beyond endothelial injury and dysfunction the number of EPCs is frequently increased and may reflect an endothelial activation. In this context, some biomarkers, i.e. vistafin/NAMT, have been discussing a promised tool to identify a pathophysiological stage of nature evolution of DM [20].

Indeed, vistafin has known as extracellular pre-B-cell colony-enhancing factor, which links adipocytokine dysfunction in T2DM/obesity, vascular damage, and endothelial dysfunction [21]. Wang et al. [22] reported that vistafin/NAMT may play a crucial role in the impaired mobilization of EPCs from bone marrow and thereby to contribute in an endothelial injury. Villalobos, et al. [23] have shown that Visfatin/NAMPT induces telomere damage and senescence in human endothelial cells. Moreover, Visfatin/NAMPT may vistafin to directly impair vascular reactivity and therefore arises as a potential new player in the development of endothelial dysfunction [21].

Whether would circulating level of vistafin/NAMT highlight a progress of DM and DM-induced vasculopathy is not fully clear, whereas decreased level of this biomarker might identify an exhausted ability of endogenous repair system in metabolic disorders including DM, metabolic syndrome and metabolically active obese [24,25]. Probably it may suggest that increased circulating level of Vistafin/NAMT is compensating response to mitigate EPC mobbing and differentiation through the NF-kappaB pathway and to attenuate vascular reparation [26-28]. It is worth noting that vistafin/NAMT is able to mediate several biological actions on endothelial directly via EPC differentiation and indirectly involving in vascular reparation vascular smooth muscle cells, metalloproteinases and growth factors [29,30]. The Figure is presented principal schema explained the role of vistafin/NAMT in endothelial repair. More clinical studies are required to evaluate the predictive role of vistafin/NAMT in DM-induced vasculopathy and worsening repair capacity (Figure 1).

In conclusion, plasma vistafin/NAMPT levels are probably indicator to distinguish of metabolically non-healthy individual at the early stage of nature evolution of the diseases. Therefore, visfatin/NAMPT could be target for therapeutic strategy aimed to improve endothelial function in T2DM patients in future.

![Figure 1](image.png)

**Figure 1** The role of vistafin/NAMT in endothelial repair and impairment.

**References**

1. Jaacks LM, Siegel KR, Gujral UP, Narayan KM (2016) Type 2 diabetes: A 21st century epidemic. Best Pract Res Clin Endocrinol Metab 30: 331-343.
2. Gruneir A, Markle-Reid M, Fisher K, Reimer H, Ma X, et al. (2016) Comorbidity burden and health services use in community-living older adults with diabetes mellitus: A retrospective cohort study. Can J Diabetes 40: 35-42.
3. Koene RJ, Prizment AE, Bлаes A, Konety SH (2016) Shared risk factors in cardiovascular disease and cancer. Circulation 133: 1104-1114.
4. Raghuraman S, Donkin I, Versteyhe S, Barrès R, Simar D (2016) The emerging role of epigenetics in inflammation and immunometabolism. Trends Endocrinol Metab 27: 782-795.
5. Berezin A (2016) Metabolic memory phenomenon in diabetes mellitus: Achieving and perspectives. Diabetes Metab Syndr 10: 176-183.
6. Berezin AE (2016) Endothelial progenitor cells dysfunction and impaired tissue reparation: The missed link in diabetes mellitus development. Diabetes Metab Syndr.
7. Berezin AE (2016) Diabetes mellitus related biomarker: The predictive role of growth-differentiation factor-15. Diabetes Metab Syndr 10: 154-157.
8. Zhang LQ, Heruth DP, Ye SQ (2011) Nicotinamide phosphoribosyl transferase in human diseases. J Bioanal Biomed 3: 13-25.
9. Imai S (2009) Nicotinamide phosphoribosyl transferase (Nampt): A link between NAD biology, metabolism, and diseases. Curr Pharm Des 15: 20-28.
10. Garten A, Petzold S, Schuster S, Körner A, Kratzsch J, et al. (2011) Nampt and its potential role in inflammation and type 2 diabetes. Handb Exp Pharmacol 203: 147-164.
11. Imai S, Yoshino J (2013) The importance of NAMPT/NAD/SIRT1 in the systemic regulation of metabolism and aging. J Diabetes Obes Metab 3: 26-33.
12. Zhou F, Pan Y, Huang Z, Jia Y, Zhao X, et al. (2013) Visfatin induces cholesterol accumulation in macrophages through up-
regulation of scavenger receptor-A and CD36. Cell Stress Chaperones 18: 643-652.
13. Kang J, Cheng B, Jiang L (2010) PPARγ signal transduction pathway in the foam cell formation induced by visfatin. Sheng Li Xue Bao 62: 427-432.
14. Romacho T, Sánchez-Ferrer CF, Peiró C (2013) Visfatin/NAMPT: An adipokine with cardiovascular impact. Mediators Inflamm 2013: 946427.
15. Kocelak P, Olszanecka-Glinianowicz M, Owczarek A, Bożentowicz-Wikarek M, Brzozowska A, et al. (2015) Plasma Visfatin/nicotinamide phosphoribosyl transferase levels in hypertensive elderly: Results from the PolSenior substudy. J Am Soc Hypertens 9: 1-8.
16. Revollo JR, Grimm AA, Imai S (2004) The NAD biosynthesis pathway mediated by nicotinamide phosphoribosyl transferase regulates Sir2 activity in mammalian cells. J Biol Chem 279: 50754-50763.
17. Garten A, Schuster S, Penke M, Gorski T, de Giorgis T, et al. (2015) Physiological and pathophysiological roles of NAMPT and NAD metabolism. Nat Rev Endocrinol 11: 535-546.
18. Berezin A, Kremzer A (2013) Analysis of various subsets of circulating mononuclear cells in asymptomatic coronary artery disease. J Clin Med 2: 32-44.
19. Berezin A (2016) Endothelial repair in diabetes: The causative role of progenitor cells dysfunction? Clin Epigen 2: 22-23.
20. Berezin AE, Samura TA, Kremzer AA, Berezina TA, Martovitskaya VV, et al. (2016) An association of serum visfatin level and number of circulating endothelial progenitor cells in type 2 diabetes mellitus patients. Diabetes Metab Syndr 10: 205-212.
21. Vallejo S, Romacho T, Angulo J, Villalobos LA, Cercas E, et al. (2011) Visfatin impairs endothelium-dependent relaxation in rat and human mesenteric microvessels through nicotinamide phosphoribosyl transferase activity. PLoS One 6: e27299.
22. Wang P, Yang X, Zhang Z, Song J, Guan YF, et al. (2016) Depletion of NAD pool contributes to impairment of endothelial progenitor cell mobilization in diabetes. Metabolism 65: 852-862.
23. Villalobos LA, Uryga A, Romacho T, Leivas A, Sánchez-Ferrer CF, et al. (2014) Visfatin/Nampt induces telomere damage and senescence in human endothelial cells. Int J Cardiol 175: 573-575.
24. Wang P, Du H, Zhou CC, Song J, Liu X, et al. (2014) Intracellular NAMPT-NAD+-SIRT1 cascade improves post-ischaemic vascular repair by modulating Notch signalling in endothelial progenitors. Cardiovasc Res 104: 477-488.
25. Gallagher KA, Liu ZJ, Xiao M, Chen H, Goldstein LJ, et al. (2007) Diabetic impairments in NO-mediated endothelial progenitor cell mobilization and homing are reversed by hyperoxia and SDF-1 alpha. J Clin Invest 117: 1249-1259.
26. Berezin A (2016) Biomarkers for cardiovascular risk in diabetic patients. Heart.
27. Lee WJ, Wu CS, Lin H, Lee IT, Wu CM, et al. (2009) Visfatin-induced expression of inflammatory mediators in human endothelial cells through the NF-kappaB pathway. Int J Obes (Lond) 33: 465-472.
28. Adya R, Tan BK, Chen J, Randeva HS (2008) Nuclear factor-kappaB induction by visfatin in human vascular endothelial cells: its role in MMP-2/9 production and activation. Diabetes Care 31: 758-760.
29. Romacho T, Aczutia V, Vázquez-Bella M, Matesanz N, Cercas E, et al. (2009) Extracellular PBEF/NAMPT/visfatn activates pro-inflammatory signalling in human vascular smooth muscle cells through nicotinamide phosphoribosyl transferase activity. Diabetologia 52: 2455-2463.
30. Fan Y, Meng S, Wang Y, Cao J, Wang C (2011) Visfatin/PBEF/Nampt induces EMMPRIN and MMP-9 production in macrophages via the NAMPT-MAPK (p38, ERK1/2)-NF-kappaB signaling pathway. Int J Mol Med 27: 607-615.