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Adipocytokines and cardiovascular diseases: putative role of Neuregulin 4

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This editorial refers to the article “Is Neuregulin-4 a predictive marker of microvascular complications in type 2 diabetes mellitus?” published by Kocak MZ *et al.* in *Eur J Clin Invest*. 2020;50:e13206.

Every year about 20 million of cardiovascular disease (CVD) new cases affect European countries [1]. Here, CVDs remain the most common causes of death accounting for about

1 every 3 cases with high variability depending on age and sex. Accordingly, adverse cardiovascular events cause about 33% of potential years of life lost (PYLL) and are the main cause of premature mortality for the male population [1]. In 2010, the World Health Organization (WHO) has set different targets for non-communicable diseases to be achieved by 2025 in order to improve global cardiovascular health. Among these, they wished a 25% relative reduction in the overall mortality from these diseases, of which CV ones account for the largest part. Yet, during the last decades, the reductions in age-standardized CVD incidence among European countries have been modest or even null [1]. Therefore, the European Cardiology Society has recently raised concern about the possibility of disregarding this ambitious goal in the member countries [1]. With diabetes being a major CV risk factor and becoming a real pandemic deeply affecting health care systems all around the word, this disease is most likely to partially account for such a failure. In addition, predictions are not at all promising: if diabetes now affects already one in 20 adults, its prevalence is forecasted to rapidly increase in the next future [1]. Thus, there is an urgent need to define new therapeutic strategies to improve CVD prevention and management. Under this point of view, the description of novel molecular targets with proven roles in the pathophysiology of CVDs and their risk factors (such as diabetes mellitus) will play a crucial role [2].

In accordance with the modern view of the adipose tissue exerting not only storage functions but being a real endocrine organ with proven roles in different physiological and pathological processes, a wide range of adipose tissue-derived mediators termed “adipocytokines” has been recently described and emerged as critical contributors and thus potential targets for different diseases [3]. Of interest, different adipocytokines produced by the dysfunctional adipose tissue have emerged as critical links between metabolic disturbances and CVD. Adipocytokines might exert different and sometimes contrasting effects on CV health with both beneficial and detrimental mediators being described [3]. Among the formers, adiponectin is the most widely investigated. It is negatively modulated in diabetes and it has been shown to be inversely associated with the protective coronary plaque features, thus promoting plaque instability and reducing CV events [4, 5]. On the other side, leptin -which is increased in the diabetic population- has been identified as a harmful mediator, predicting the presence of coronary plaques,

and the occurrence of acute CV events and their severity [6-8]. For other adipocytokines (e.g. resistin, lipocalin-2 and visfatin), the relationship is not yet clear and further studies are needed in order to delineate their potential effect on CV [3, 9, 10]. Among these, the newly described Neuregulin 4 (Nrg-4) is mainly produced by the brown adipose tissue and belongs to the neuregulin family of epidermal growth factor that holds important functions in cellular proliferation, migration and differentiation. Of interest, Nrg-4 levels have been reported to be modulated by different metabolic afflictions including type 2 diabetes mellitus, insulin resistance and obesity [11, 12], thereby suggesting a role for this adipocytokines in the pathophysiology of such diseases and their vascular complications. Yet, few studies have so far investigated the relationship between Nrg-4 and CV homeostasis and diseases thus, its role remains to be fully understood. An interesting study recently published by Kocak MZ *et al.* in the *European Journal of Clinical Investigation* added a piece of knowledge to the field by probing circulating Nrg-4 levels in patients with type 2 diabetes mellitus and correlating them with the presence of microvascular diabetes complications) [13]. In their retrospective study of 89 diabetic individuals consecutively enrolled at the University Hospital of Bolu (Turkey), Nrg-4 was significantly reduced by ~2 times in patients presenting retinopathy, neuropathy or nephropathy [13]. In particular such a difference was greater when comparing patients with or without neuropathy than those with nephropathy or retinopathy. Nrg-4 levels showed a negative correlation with fasting glucose, glycated hemoglobin and microalbuminuria in the whole population while a positive regulation was shown with high density lipoprotein cholesterol (HDL) [13]. The logistic regression analysis showed Nrg-4 to be a protective factor associated with reduced presence of diabetes complications (odd ratio: 0.527, 95% confidence interval: 0.336-0.825, p= 0.005) even when considering age, gender, diabetes duration, fasting glucose, glycated hemoglobin, HDL and creatinine as covariables. Finally, ROC curves analysis suggested Nrg-4 the predictive ability of Nrg-4 on the presence of microvascular diabetes complications with 1.42 ng/mL being the best cut-off value determined by Youden's index [13]. Although the study finds important limitations in its retrospective single-center design, low number of patients and poor definition of endpoints, the authors provided a first hint into the potential of Nrg-4 as a biomarker for the early detection of diabetes microvascular

compliances. Finally, this study fosters further investigation to detail the pathogenic mechanisms linking diabetes, Nrg-4 and vascular health.

Mechanistically, Nrg-4 is synthesized as a trans-membrane protein which is then released in the circulation by proteolysis. Both forms act specifically through ErbB-4 receptor tyrosine kinases and activating phosphatidyl inositol 3 kinase (PI3K) and mitogen-activated protein kinase (MAPK) intracellular signaling pathways [14]. Experimental models of metabolic syndrome have suggested Nrg-4 to improve glucose homeostasis, preserve lipid homeostasis, blunt insulin resistance and gain of weight. In the liver, Nrg-4 attenuates hepatic lipogenesis and stress-induced hepatocyte apoptosis thereby preventing diet-induced nonalcoholic steatohepatitis [15, 16]. Furthermore, Nrg-4 was shown to play role in regulation of diet-induced chronic low-grade inflammation by reducing macrophage infiltration and activation within the adipose tissue [16]. Interestingly, chronic low-grade inflammation is the hall-mark of metabolic disturbances and has emerged as an important mediator of their CV compliances [17, 18]. Previous reports showed that circulating Nrg-4 is downregulated in patients with metabolic syndrome and that it inversely correlates with carotid intima-media thickness, a marker of subclinical atherosclerosis [19, 20]. Also, reduced Nrg-4 levels have been shown to predict the presence of coronary artery disease independently of blood pressure, lipid levels and smoking habits indicating Nrg-4 as a possible residual risk factor for atherosclerosis [21]. Yet, the specific mechanisms by which Nrg-4 exerts its protective role on vascular homeostasis remain to be fully elucidated. Under this point of view, ErbB4 signalling has been shown to attenuate neo-intima formation in a rat carotid artery injury model, where Nrg4 resulted overexpressed [22]. Also, ErbB4 activation activates the Akt/PI3K pathway that holds well-known protective features in endothelial cells where it inhibits apoptosis and exerts anti-atherosclerotic effects [23, 24]. Such indirect findings further underlined the potential protective role of Nrg-4 on vascular tissue which can be impaired during metabolic disturbances thus contributing to the development of CVD. Further clinical and experimental studies are needed to confirm the protective role of this new adipocytokine in the context of CVD and delineate its pathophysiological role to enable the development of therapeutics targeting its reduction.

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Conflict of interests

None.

Authors' contributions

All authors equally contributed to the manuscript and approved its final version.

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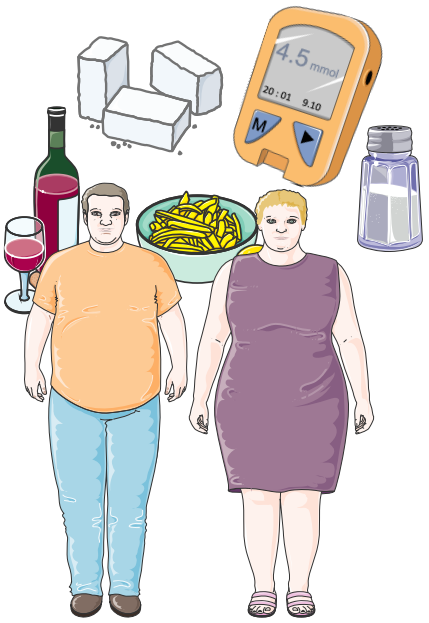
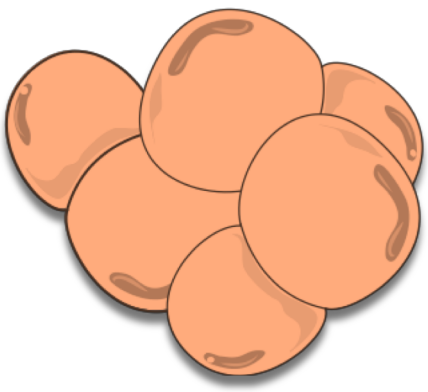
Figure legend

Figure1: Suggested mechanisms for the protective effect of Neuregulin 4 on the pathophysiology of cardiovascular diseases. Metabolic disturbances such as diabetes mellitus reduce circulating levels of neuregulin 4 that is produced mainly by the brown adipose tissue. Since neuregulin 4 may play a protective role on the vascular endothelium by reducing its dysfunctional activation and apoptosis, pathologic reduction of such a beneficial mediator may at least partially account for the increased cardiovascular risk of these patients. MAPK: mitogen-activated protein kinase; PI3K: phosphatidyl inositol 3 kinase.

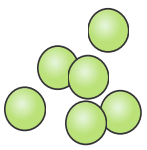
Figure 1

Diabetes mellitus
Metabolic syndrome
Overweight/obesity

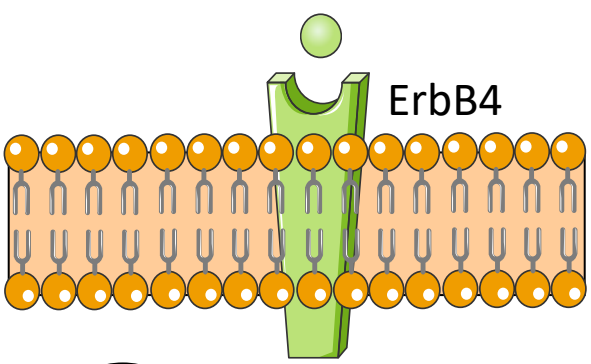




Brown adipose tissue



Neuregulin 4



Akt/PI3K
MAPK

Vascular endothelium

Dysfunctional activation
Inflammation
Oxidative stress
Apoptosis
Atherogenesis
CV disease