Review Article

Integrative Diabetes and Cardiovascular Diseases

Homocysteine Levels Otherwise Display Cardiovascular Disease in Diabetes Mellitus

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Abstract

Patients suffering for Diabetes Mellitus (DM) have 2 to 6-fold increase of cardiovascular complications. On the other hand, serum increase of total plasma homocysteine (HHcy) is an emerging risk factor for Cardio-Vascular Disease (CVD). A stronger association between DM and HHcy exists, even through the underlying pathogenetic mechanism remains unexplained. Thus, patients contemporary having DM and HHcy have a prevalence of CVD, whereas in those without HHcy, metabolic symptoms often prevail on cardiovascular complications. The possible causes of higher incidence of CVD in DM and HHcy in comparison to DM without HHcy were examined. The different Resistin expression from adipocytes between DM with and without HHcy seems to unlikely influence the incidence of CVD. Concerning that, two different variants of DM may be identify: one, characterized by prevalent metabolic symptoms (dysmetabolic form) and another, characterized by early and massive atherosclerotic symptoms (cardiovascular form).

Keywords: Diabetes mellitus; Homocysteine; Resistin; Cardiovascular disease

Background

Cardiovascular complications are constantly present in type 2 diabetes mellitus (T2DM) and are the main cause of morbidity and mortality in these patients [1]. But, cardiovascular impairments differently characterize diabetic individuals. In fact, metabolic disorders prevail in some, whereas cardiovascular diseases (CVD) are prevalent and chiefly present in others. The different clinical manifestations of T2DM must be probably reported to the unlike Resistin expression. The main micro-and-macrovascular complications of T2DM are reported in table 1.

Resistin

Resistin for "resistance to insulin" is a peptide hormone secreted by adipocytes of adipose tissue, but also found in mononuclear leukocytes, macrophages, spleen and bone

marrow cells [2-4]. Normally, its serum concentration in humans ranges from 7 to 22 ng/ml. It has been suggested that the hormone is involved in the pathogenesis of obesity, insulin resistance and T2DM [3-6]. Particularly, administration of Resistin impairs glucose tolerance and insulin action in mice, whereas anti-resistin antibody improves hypoglycemia and reduces insulin resistance. In addition, changes in the mass and metabolism of adipose tissue may be related to insulin resistance and obesity, commonly associated to T2DM. But, Resistin has also been associated to the development of atherosclerosis, endothelial dysfunction, thrombosis and CVD, non-alcoholic fatty liver disease, inflammation, asthma and malignancies. These evidences suggest that Resistin plays a role in the pathogenesis of obesity, insulin resistance and T2DM [7-9]. But, the peptide hormone also comes into pathogenesis of CVD [10].

Table 1: Vascular complications in diabetes mellitus.

Micro-vascular	Macro-vascular
Nefropathy	Myocardial infarction
Neuropathy	Ischemic stroke
Retinopathy	Peripheral artery disease

Table 2: Serum concentrations of Homocysteine.

Normal range	5-9 μ mol/L
Borderline	10-12 μ mol/L
Light HHcy	13--30 μ mol/L
Moderate HHcy	30-100 μ mol/L
Severe HHcy	>100 μ mol/L

Table 3: Leading inherited and acquired factors inducing an increased Hcy levels.

Inherited
Deficiency of MTHFR
Deficiency of CBS
Acquired
Diet-deficit of Vitamins 6-9-12
Anaemia perniciosa
Chronic renal failure
Hypothyroidism
Some cancers
Psoriasis severe
Drugs
Metformin
Thiazides
Caffeine
Fenofibrate
Levodopa
Anticonvulsants
Methotrexate
Niacin
Cholestiramine
Lifestyle
Chronic alcohol consumption
Excessive coffee consumption
Lack of exercise
Smoking

Resistin and CVD

Although more controversies still exist about the exact mechanisms by which Resistin favours CVD, recent studies suggest that the hormone directly causes endothelial dysfunction, via down regulation of cellular

eNOS and increased production of pro-oxidant ROS. As previously affirmed, Resistin favours atherosclerosis. This effect happens by increasing the expression in human endothelial cells of pro-inflammatory cytokines. In turn, these promote monocyte/macrophage recruitment and

adhesion to endothelial cells, including MCP-1, ICAM-1 and VCAM-1. Furthermore, Resistin appears to be involved in thrombosis, platelets' aggregation, vascular smooth muscle cells migration/proliferation and cholesterol metabolism [11-13].

Homocysteine

Homocysteine (Hcy) is a sulfur-containing amino acid derived from the metabolism of methionine (Met). The levels of Hcy can be increased by defective metabolism of Met, resulting from either mutation in genes coding for the enzymes of Hcy metabolism [14,15] or deficiencies of certain vitamin cofactors [16]. Apart from defects in the enzymes of Hcy metabolism (that are inherited), HHcy can also be induced by dietary manipulations. These include enrichment of diet with Met or depleting diets with vitamins folate or B₆ or B₁₂ [17]. The normal values of Hcy and its increased serum levels were reported in table 2.

In addition to genetic variations, vitamin deficiencies, and several other environmental factors, such as increased intake of Met, certain medications, disease state elderly, pregnancy and/or lactation can contribute to variations in Hcy levels [18,19]. In table 3 were summarized the leading factors inherited and acquired inducing a condition of HHcy.

HHcy besides acts a potent pro-inflammatory factor and, likewise to Resistin, promotes atherosclerotic lesions [20,21]. This effect largely derives from mechanisms Resistin-independent [22]. But, a significant association between HHcy and insulin resistance (and therefore of Resistin) was also found [23-25]. Particularly, elevated Hcy levels generates Reactive Oxygen Species (ROS) that weaken the function of insulin secreting cells, generating insulin-resistance. This leads to reduced glucokinase phosphorylation and reduced secretion function, leading to a cell death [26]. Of consequence, the increased Hcy levels may also act on cardiovascular system by Resistin. This suggests that the association of HHcy with diabetes only happens in T2DM, having still preserved secretory functional pancreas with insulin resistance, whereas in type 1 diabetes mellitus (T1DM) without insulin production, plasma concentration of Hcy is normal or low. Concerning this issue, Li et al. firstly demonstrated that HHcy increases Resistin expression and secretion from adipocytes, via ROS-PKC-NFκB pathway and subsequently promotes insulin resistance both in vitro and in vivo, probably evolving in T2DM [27]. We also have reported a possible link between Hcy and insulin resistance [28].

CVD in patients with diabetes and HHcy

Therefore, the contemporary presence of T2DM in patients with HHcy is a clinical condition in which both metabolic and cardiovascular impairments due to the Resistin are intensified. This condition comes because HHcy and T2DM have a synergistic negative cardiovascular effects [29], that must be reported to increased Hcy serum levels alone and Resistin (expressed in bigger amount in T2DM patients with HHcy than in those without) [30]. Previously, Buysschaert et al. have described a higher prevalence of vascular complications, such as macroangiopathy and microangiopathy and nephropathy in diabetics with HHcy in comparison to the patients affected by diabetes with normal Hcy concentration [31]. Hoogeveen et al. have reported an increased mortality due to CVD in the population of diabetics with high Hcy levels [32]. A classical example of macroangiopathy is coronary atherosclerosis characterized by formation of plaques in the coronary arteries, while microangiopathy is exemplified in nephropathy or in retinopathy and due to endothelial lesions, interstitial fibrosis and matrix increased [33].

Conclusions

As previous affirmed, Resistin is a peptide clearly increased in obese patients affected by T2DM with HHcy, in comparison to diabetics without increased Hcy levels. Several evidences suggest that the raised hormone-concentration is a more important determinant of CVD in diabetes mellitus. The display of these precociously complicates the symptoms and the evolution in diabetics with HHcy and their manifestations are prevalent on the metabolic symptoms. Therefore, the variable Resistin expression connected to the presence or the absence of HHcy in T2DM, shapes two unlike presentations and evolutions of T2DM. Of these, cardiovascular variant prevails in T2DM with HHcy, whereas metabolic derangements are more evident in T2DM without HHcy [34]. But, the detailed mechanisms for the interaction between diabetes mellitus and increased Hcy levels into induce CVD, even through reported to greatest Resistin expression are still not well known.

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