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Insulin Resistance, with or without Diabetes Mellitus, in Hyperhomocysteinemia Worsens Atherosclerosis

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Abstract

Background: Increased homocysteine levels cause the secretion of Resistin, a peptide hormone responsible for insulin resistance with or without type 2 diabetes mellitus. It is known that HHcy is a risk factor for atherosclerosis independently from T2DM. On the other hand, insulin resistance, especially evolving towards T2DM, favors per se cardio-vascular atherosclerotic injuries independently from metabolic derangement.

Methods: Independently of metabolic changes, both HHcy and T2DM are responsible for an increased risk of atherosclerosis. Several mechanisms of two defective metabolic diseases act in ways that are partly similar and partly different.

Results: The coexistence of HHcy and insulin resistance, especially T2DM, strengthens the incidence of atherosclerotic lesions in patients suffering from both HHcy and insulin resistance at the same time.

Conclusion: The contemporary presence of HHcy and T2DM often exists, even if the causes are still unknown. It increases cardio-vascular atherosclerotic changes respect to the single metabolic disease.

Keywords: Hyperhomocysteinemia; Insulin resistance; Resistin; Type 2 Diabetes Mellitus; Atherosclerosis

Introduction

Some studies report that elevated levels of serum Homocysteine (Hcy) are associated with Insulin Resistance (IR), with or without Type 2 Diabetes Mellitus (T2DM) [1-3], and atherosclerotic complications [4]. A recent meta-analysis of Wang et al. [5] revealed that Hcy levels in patients with T2MD were higher than health individuals, especially in those with Diabetic Nephropathy (DN) or Diabetic Retinopathy (DR). Previously, other reports have debated about a possible link between Hcy levels and insulin resistance and the effects of folic acid and vitamin B12 supplementation on vascular damage [6]. Another report confirms the incidence of diabetic cardiovascular disease in patients suffering from increased Hcy (HHcy) [7]. In a study performed in rodents, Li et al. [8] found that Resistin (R), a peptide hormone secreted by adipose tissue, is involved in insulin resistance and responsible for hyperglycemia. The hormone is also present in mononuclear leukocytes, spleen, and bone marrow cells [9]. Thus, a link between adipocytes and diabetes exists. On the other hand, in humans, macrophages (like adipocytes) have been found to be an important source of R [10]. The relationship between HHcy and IR seems to be due to the over-expression of R from adipose tissue, *via* Endothelial Reticulum Stress (ERS) [11]. Specifically, HHcy is responsible of the production of inflammatory cytokines, as Interleuchin-6 (IL-6), Interleukin-1β (IL-1β), Tumor Necrosis Factor-α (TNF-α) and facilitating macrophage infiltration. That provokes the R expression through the activation some kinases [9,10]. In turn, R causes obesity and IR considered a chronic inflammatory status (Figure 1) [12].

It must be added that R is also associated with the development of atherosclerosis, endothelial dysfunction, cerebral and/or cardiac thrombosis, peripheral vascular diseases, inflammation and some malignancies and metastases [13-16]. But a novel mechanism responsible for IR in presence of HHcy was suggested. It consists in the change of cysteine-825 of proinsulin receptor that induces IR and type 2 diabetes phenotype *via* protein cysteine-homocysteinylation [17].

T2DM related to IR is a metabolic disease characterized by persistent hyperglycemia due to

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the impaired (reduced) insulin secretion and inappropriate glucagon secretion, with other possible metabolic alterations. It may cause some damages of various organs and systems, leading to several health complications. Micro- and macro-vascular diseases increase of (2-6) folds in comparison to non-diabetic population. These are commonly present in persons older than 45 years [18]. Herein, we discuss about the frequency and the incidence of vascular (atherosclerotic) risk derived by the contemporary presence, in the same patient, of HHcy and T2DM.

Hcy is a sulfur-containing amino acid, as intermediate product of Methionine (Met), through the re-methylation pathway [19]. The end products of Hcy transsulfuration are Cysteine and Glutathione [19]. Both re-methylation and transsulfuration provide to inhibit the serum accumulation of Hcy, called HHcy (Figure 2) [20].

HHcy + IR

Some studies reported a positive correlation between HHcy and IR, with or without T2DM [21-23]. On the contrary, the Prospective Investigation of the Vasculature study in Uppsala Seniors (PIVUS) showed no evidence of plasma HHcy associated with T2DM [24]. At present, it was demonstrated that inflammatory cytokines produced by adipocytes, through ERS, induce the over-expression of R, responsible for both obesity and IR [5]. IR, in turn, may cause a state of pre-diabetes or can evolve towards clinical T2DM. Nevertheless, the incidence of T2DM in patients with HHcy is still unknown [25]. Concerning this, several studies found that patients contemporarily suffering of HHcy and T2DM may have an increased risk of atherosclerosis [25-27]. It is known that the increased Hcy levels or T2DM, separately, are responsible for atherosclerosis. Likely, when these two findings are contemporarily present, atherosclerosis is accelerated.

HHcy-risk factors

HHcy is recognized as a risk factor for several conditions responsible for atherosclerosis (Figure 3) [28]. It induces endothelial dysfunction, early responsible for thrombogenicity through the reduction of Nitrogen Monoxide (NO), a powerful vasodilator factor produced by the endothelial NO synthase [29-31]. The reduction happens *via* Asymmetric Dimethylarginine (ADMA), an endogenous inhibitor of NOS [32]. In turn, ADMA concentration rises for decreased activity of the enzyme Dimethylarginine Dimethyl-Amino-Hydrolase (DDAH) which metabolizes ADMA [33-34]. Furthermore, the alteration of endothelial and smooth muscle cells is responsible for accelerated Reactive Oxygen Species (ROS) formation [35]. That happens because of decreased expression and/or activity of key oxidant enzymes as well as increased enzymatic generation of superoxide anion. Apart for directly activating platelets, these increase their adhesion to the vascular endothelium. HHcy also favors thrombogenicity by ROS, decreasing extracellular nucleotide hydrolysis, as evidenced in rat platelets [36]. Concerning this, Lentz demonstrated a significant decrease in thrombomodulin anticoagulant activity [37]. Signorello et al. [38] affirm that in platelets, HHcy induces release of arachidonic acid to generate thromboxane A, that activates the platelets. Increased production of ROS is responsible for oxidative stress, considered as an imbalance between ROS and the ability of a biological system to detoxify these products. A body of evidence demonstrated that oxidative stress can be responsible a risk factor for some important disorders, such as inflammatory diseases, including cardiovascular disease, stroke, diabetes mellitus, renal failure, and cancer [39]. This happens *via* oxidative stress, that impairs the ability of endothelial cells to release NO, contributing to the endothelial dysfunction [39]. Moreover, activated endothelial cells have been shown to upregulate the adhesion molecules. These are responsible for monocytes and Vascular Cell Adhesion Molecule-1 (VCAM-1) production, release of some cytokines, chemokines, Interleukin-1 (IL-1), Interleukin-6 (IL-6), Interleukin-8 (IL-8), Macrophage-Chemoattractant Protein-1 (MCP-1) and TNF-α [40,41]. In addition, HHcy induces the association with hyperlipemia, favoring the atherosclerotic findings [42]. Particularly, HHcy is frequently associated with total cholesterol and Low-Density Lipoproteins (LDL)- cholesterol, often evident in aged patients contemporarily suffering from HHcy and T2DM. Apart from atherosclerosis, the increased values of cholesterol

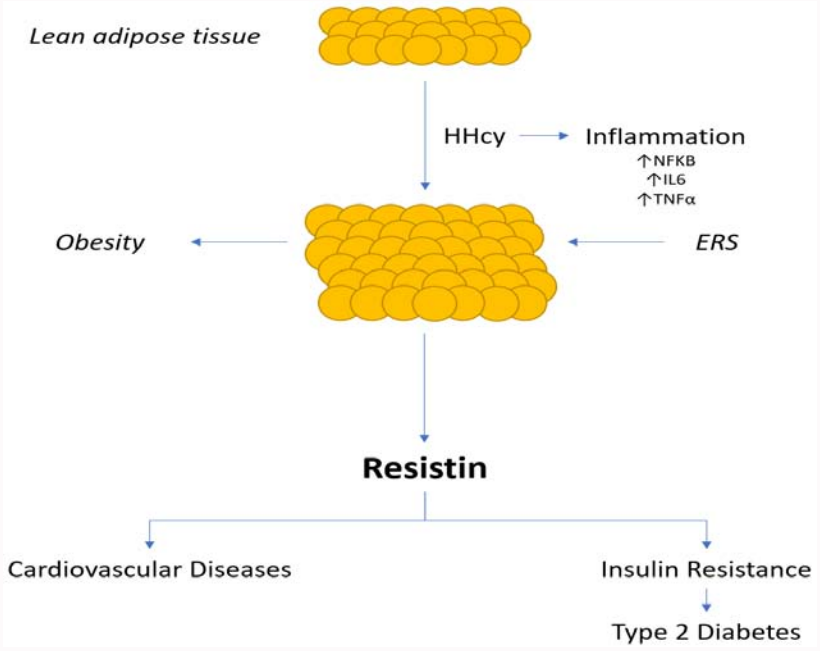

Figure 1: Resist in secreted by adipose tissue induces insulin resistance and some cardiovascular diseases.

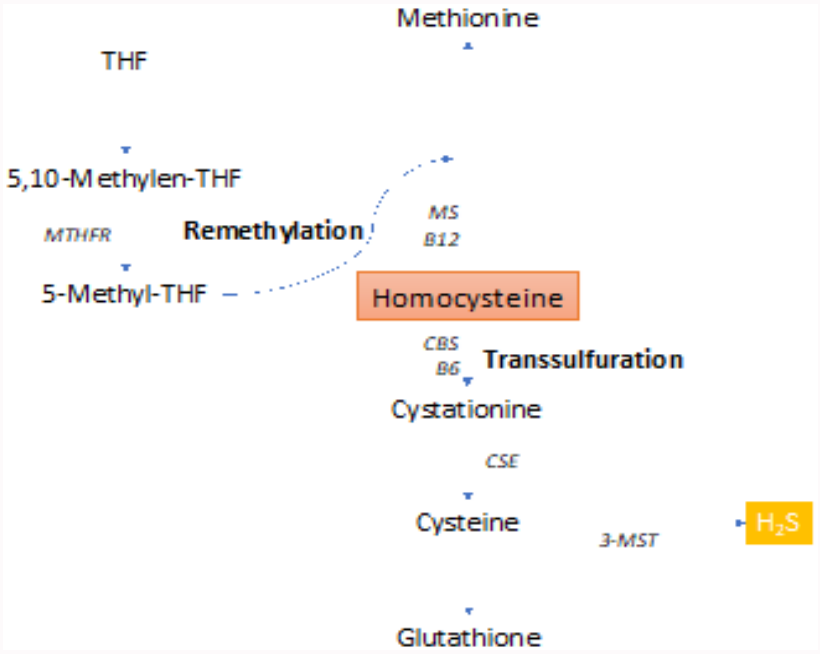

Figure 2: Homocysteine metabolism through the remethylation and transsulfuration pathways.

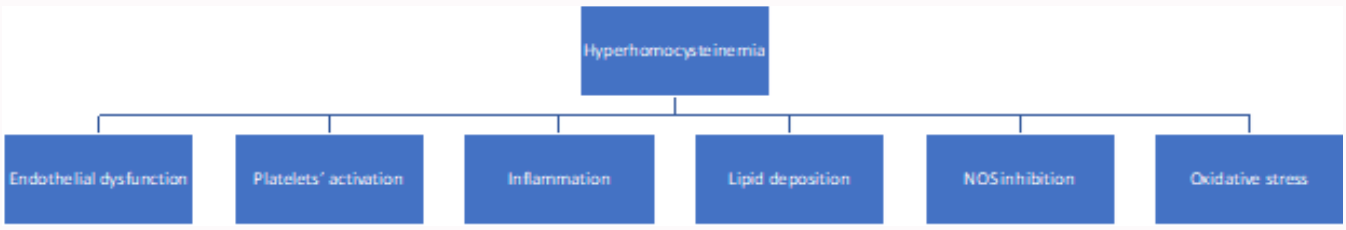

Figure 3: Main mechanisms through hyperhomocysteinemia induces atherosclerosis.

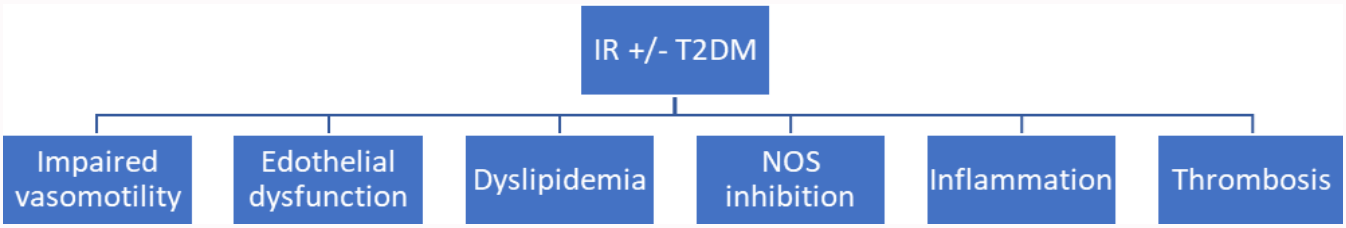

Figure 4: Some mechanisms induced by Insulin Resistance (IR)/Type 2 Diabetes Mellitus (T2DM) favoring atherosclerosis.

and phospholipids play a key role in the normal function of cells' membrane [43]. The hypomethylation HHcy is a major responsible for increased lipids accumulation. Particularly, that happens for DNA hypomethylation prevalently carried out in the liver [44,45]. Finally, HHcy causes the dysfunction of Matrix Metalloproteinase (MMP) independently of atherosclerosis [46]. The phenomenon happens because of a decreased elastic compliance of the vessel wall through NO isoforms (NO synthase, endothelial NO, inducible NO) [47]. In turn, MMP dysfunction of the aortic wall can induce a non-frequent and dreadful clinical complication, such as Abdominal Aortic Aneurysm (AAA), often evolving towards its rupture or inside thrombus formation [48].

IR/T2DM-risk factors

IR is a condition in which muscles, liver and fat don't respond correctly to the action of insulin for glucose use. The syndrome includes obesity, hypertension, hypercholesterolemia and T2DM (metabolic syndrome) [49]. IR begins the atherosclerotic process *via* several mechanisms (Figure 4), such as impaired vasomotility, oxidative stress, increased serum levels of Very Low-Density Lipoproteins (VLDLs), triglycerides, and low-density LDLs-cholesterol [50]. Dense LDL present in patients with IR and/or T2DM are strongly predictive of atherosclerotic events. These enter the arterial wall, causing toxic effect of endothelial cells. In addition, the oxidation of LDL lipoproteins, deriving by ROS formation and Reactive Nitrogen Species (RNS), has a crucial role in the initiation and development of atherosclerosis. That induces an endothelial dysfunction and Vascular Smooth Muscle Cells (VSMCs) proliferation, while LDL accumulation leads to foam cells formation, further favoring the atherosclerotic lesions [51,52].

Referring to the vascular endothelium, it is known that this is an

endocrine organ involved in the regulation of vascular tone. It plays a fundamental role in the maintenance of vascular homeostasis. The function depends on production of some mediators able to regulate vascular tone. The balance among endothelium-derived vasodilative substances (NO, prostaglandins, derived hyperpolarization factor, etc.) and vasoconstrictors (Angiotensin II, prostanoids, isoprostanes) is responsible for the normal vascular contractility, while the prevalence of vasodilative factors on vasoconstrictors or *vice versa* causes an impaired vascular tone. In addition, the vasodilator factors have anti-proliferative and anti-inflammatory effects, while the vasoconstrictors are mitogenic and favor the inflammation. Mitogen activity consists in the proliferation of VSMCs, responsible of vascular wall's fibrosis, while the inflammatory activity causes the production of proinflammatory cytokines, growth factor, interleukins and others. Particularly, cytokines are associated with vascular dysfunction and atherosclerosis, abdominal aortic aneurysm, and systemic hypertension [51]. These activities contrast with normal endothelial function, reduce the expression of vascular cell adhesion molecules, attenuate the production of proinflammatory cytokines, decrease leukocytes recruitment, inhibit VSMC proliferation, attenuate platelet's aggregation and reduce monocytes adhesion [53-57]. Therefore, while the normal endothelial function depends on insulin sensitivity, endothelial dysfunction is strongly favored by IR [58,59]. Finally, in these patients, metabolic disorder disturbs the physiological balance of coagulation and fibrinolysis. Specifically, hyperglycemia and IR upregulate level of the pro-coagulation mediators, like tissue factor, thrombin and some coagulative factors, such as FVII, FXI, FXII, etc. On the other hand, diabetes contributes to cardiovascular changes and reduces fibrinolysis by decreasing tPA and increasing PA-I, contributing to generate clots [60-63]. Other factors frequently present in diabetic patients, such as obesity and dyslipidemia, also contribute to coagulation disorders and are prone to thrombus generation [63-67].

Conclusion

Conclusively, the coexistence of HHcy and IR with or without T2DM and obesity, significantly increases atherosclerotic changes through several mechanisms. Among possible mechanisms of increased atherosclerotic stigmata rising from the coexistence of two defective metabolic syndromes are included the inflammatory status and the increased procoagulant activity, especially in diabetic nephropathy, and endothelial dysfunction. It must be also added that cardiovascular changes happening in these patients aren't just the number of atherosclerotic marks induced by HHcy and IR separately esteemed, but a strengthened result derived by the contemporary presence of two metabolic disorders. But the modalities through both HHcy-factors and IR-factors contemporarily act in induce and accentuate atherosclerotic cardio-vascular derangement act are still unknown.

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