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The interaction of choline and one-carbon / folate metabolism derangements on the cardiac remodeling process with or without diabetes

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Abstract

Proper nutrition helps protect from illness and disease. Choline (Ch), an essential molecule of substantial importance for the optimal development and function of several biological systems, plays a crucial role in the pathway of one-carbon metabolism. On the other hand, Ch-deprivation (CD) has been linked with abnormal fat metabolism, insulin resistance, and myocardial dysfunction. The Ch-deficiency setting is an established experimental model of non-alcoholic steatohepatitis that resembles the human non-alcoholic fatty liver disease (NAFLD); a disease with constantly increasing incidence and prevalence. NAFLD, commonly associated with metabolic comorbidities such as obesity and type 2 diabetes mellitus, consists a high risk for cardiovascular disease. Experimental data of dietary CD through the administration of a Ch-deficient diet to rodents have revealed myocardial monocyte infiltration along with cardiac interstitial oedema and fibrosis, as well as a deleterious effect on cardiac valves that could lead to impaired heart mechanical properties which resemble to a restrictive pattern of cardiomyopathy characterised mainly by diastolic dysfunction. In a Ch-deprived diabetic experimental model, the diastolic heart failure has been characterized by a concentric hypertrophied myocardium, a left ventricular cavity with a thinner wall, and an increased left ventricular diastolic diameter, in addition to a left atrial dilatation that could also exert functional derangement and provoke arrhythmogenesis, thereby jeopardising cardiac output.

KEYWORDS

choline-deprivation, diabetes, diabetic cardiomyopathy, rat

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MAIN MESSAGE

Proper nutrition helps protect from illness and disease. Choline (Ch), a water soluble vitamin B co-factor, is an essential nutrient for which dietary intake recommendations have been established by the Institute of Medicine since 1998 and by the European Food Safety Authority since 2016. Ch is an intrinsic component of a number of important biomolecules, has a vital role in the one-carbon cycle by facilitating the metabolism of methyl groups,

and is also involved in cellular membrane integrity, in metabolic reactions (as methyl-donor), as well as in the biosynthesis of different macromolecules (including phospholipids and acetylcholine) [1].

On the other hand, Ch-deprivation (CD), observed either in physiological (pregnancy and lactation) or pathological (alcoholism and malnutrition) conditions, has attracted much consideration due to its association with various adverse health impacts that can occur across the lifespan. Prolonged CD causes decreased tissue S-adenosylmethionine levels, global DNA hypomethylation, and may lead to hepatocellular modifications and fatty liver induction [2,3]. The CD setting is an established experimental model of non-alcoholic steatohepatitis that resembles the human non-alcoholic fatty liver disease (NAFLD); a disease with constantly increasing incidence and prevalence. NAFLD, commonly associated with metabolic comorbidities such as obesity and type 2 diabetes mellitus, consists a high risk for cardiovascular disease [4].

Experimental data of dietary Ch-deprivation through the administration of a Ch-deficient diet to rodents have revealed myocardial monocyte infiltration along with cardiac interstitial oedema and fibrosis, as well as a deleterious effect on cardiac valves accompanied by concordant functional changes (i.e., impaired left ventricular contractility and diastolic function, probably due to reduced compliance of the myocardium) [5], and increased B-type natriuretic peptide levels that could be related to the impaired mitochondrial fatty acid oxidation. The dysregulation of matrix metalloproteinases (MMPs), more specifically of MMP-2 and MMP-9, and of their inhibitors that have been shown to be predominately responsible for cardiac matrix homeostasis [6], are probably among the factors contributing to myocardial dysfunction [7]. Furthermore, CD has been shown to modulate myocardial acetylcholinesterase (AChE) and important adenosine triphosphatase (ATPase; namely, Na^+,K^+-ATPase and Mg^{2+}-ATPase) activities [8]. Na^+,K^+-ATPase is an ion pump crucial for the electrochemical gradient maintenance and cardiomyocyte repolarization; it functions at the expense of cell energy expenditure, has the ability to alter multiple signalling cascades [9], and secondarily facilitates the transport of nutrients into the cell. On the other hand, Mg^{2+}-ATPase is believed to affect the activity of Ca^{2+}-ATPase in the membrane, thereby maintaining normal Mg^{2+} levels within the myocytes, which is vital for the contraction and relaxation cycles of the cardiac muscle. Furthermore, Ch is a precursor of acetylcholine; a basic neurotransmitter of the autonomous nervous system that regulates chronotropic and dromotropic responses of the heart. AChE, the enzyme responsible for acetylcholine degradation (as it terminates cholinergic neurotransmission), also plays a key role in the regulation of the parasympathetic tone of the heart, as one of the main compensatory mechanisms in heart failure is the shift of the sympathetic - parasympathetic equilibrium in favour of the sympathetic nervous system. Moreover, the local activity of AChE can influence the metabolic state of the cardiomyocytes.

In a Ch-deprived experimental model, the diabetic myocardium has been characterized by aggravation of inflammation and fibrosis, as well as by stiffness as a result of CD, which in turn has been associated with the up-regulation of the vascular endothelial growth factor expression in the myocardium and with an impaired structural morphology of the latter. More specifically, there has been evidence of a dilation of the left heart cavity as demonstrated by a concentric hypertrophied myocardium, a thinner left ventricular cavity wall and an increased left ventricular diastolic diameter. The significantly higher myocardial ejection velocity (associated with left ventricle's wall tension index) in addition to the left atrial dilatation could also exert functional derangement and provoke arrhythmogenesis, which, in turn, jeopardises cardiac output [10].

In conclusion, the Ch-deprived diabetic heart seems to arise as a new distinct phenotype of cardiomyopathy that simultaneously combines features of the restrictive and the dilated type.

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CONFLICT OF INTEREST STATEMENT

The author declares no conflicts of interest.

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