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Review

Macro- and micronutrient dyshomeostasis in the adverse structural remodelling of myocardium

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Hypertension and heart failure are worldwide health problems of ever-increasing proportions. A failure of the heart, during either systolic and/or diastolic phases of the cardiac cycle, has its origins rooted in an adverse structural, biochemical, and molecular remodelling of myocardium that involves its cellular constituents, extracellular matrix, and intramural coronary vasculature. Herein we focus on the pathogenic role of a dyshomeostasis of several macro- (i.e. Ca^{2+} and Mg^{2+}) and micronutrients (i.e. Zn^{2+}, Se^{2+}, and vitamin D) in contributing to adverse remodelling of the myocardium and its failure as a pulsatile muscular pump. An improved understanding of how these macro- and micronutrients account for the causes and consequences of adverse myocardial remodelling carries with it the potential of identifying new biomarkers predictive of risk, onset and progression, and response to intervention(s), which could be monitored non-invasively and serially over time. Moreover, such incremental knowledge will serve as the underpinning to the development of novel strategies aimed at preventing and/or regressing the ongoing adverse remodelling of myocardium. The time is at hand to recognize the importance of macro- and micronutrient dyshomeostasis in the evaluation and management of hypertension and heart failure.

1. Introduction

An adverse structural remodelling of myocardium, involving cellular constituents of its muscular, intramural coronary vascular, and interstitial compartments, contributes to the heart's failure as a muscular pump during either systolic or diastolic phases of the cardiac cycle. The elucidation of molecular mechanisms involved in the pathogenesis of such remodelling, including those contributing to its progressive nature, are of considerable importance and the subject of ongoing research. Herein, we provide our perspective as to the role of macro- and micronutrient dyshomeostasis in promoting such adverse remodelling.

Macronutrients are chemical elements essential to life in large quantities. Calcium and magnesium are macronutrients (or macrominerals) available in milligram quantities and must be obtained from the environment. Micronutrients are present in microgram quantities. They too are essential, must be derived from external sources, and are integral components of enzymes or coenzymes involved in chemical reactions. Reduced circulating levels of such micronutrients as Zn^{2+} and Se^{2+}, together with macronutrients, expressed as ionized hypocalcaemia and hypomagnesaemia, are found in patients with either hypertension or congestive heart failure (CHF), irrespective of race, ethnicity, or the aetiological origins of the failing heart.[1–8] Increased excretory losses of Ca^{2+}, Mg^{2+}, and Zn^{2+} accompany pharmacological agents commonly used in the management of hypertension or CHF, including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and loop diuretics.[9] Symptomatic heart failure with reduced effort tolerance will constrain such patients to a housebound lifestyle deprived of sunlight. Thus, hypovitaminosis D is a common finding in these patients.[7,8,10–12] This is especially the case in people with dark skin, where melanin is a natural sunscreen mandating longer exposure to the UVB component of sunlight for the skin to begin the process leading to vitamin D steroidogenesis.[13] Hence, a deficiency of multiple macro- and micronutrients is an important accompaniment of hypertension and CHF. Each has the potential to adversely influence the structure of the failing myocardium.

Herein, we focus on a dyshomeostasis of Ca^{2+}, Mg^{2+}, Zn^{2+}, Se^{2+}, and vitamin D and their contribution to a remodelling of myocardial structure. Importantly, these nutrients

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are closely linked to one another and, therefore, no single entity would appear more important than another. Intracellular Ca^{2+} overloading, for example, is coupled to increased intracellular Zn^{2+} entry, while Mg^{2+} is a physiological antagonist of cellular and mitochondrial Ca^{2+} entry. The significance of these divalent cations and vitamin D is underscored by their pathophysiological roles in the appearance of oxidative stress in diverse tissues, and to the overall activity of antioxidant defenses found at these sites.

2. Polynutrient dyshomeostasis in hypertension and congestive heart failure

The importance of oxidative stress in the remodelling of the myocardium, where reactive oxygen (ROS) and nitrogen species (RNS) overwhelm antioxidant defenses and contribute to its progressive nature, has come to light in recent years. Moreover, the altered redox state appears concurrently in such diverse tissues as skin, muscle, peripheral blood mononuclear cells (PBMCs), and blood, which underscores its systemic nature. Collectively, these findings call into question the potential role of macro- and micronutrients involving diverse tissues, including the heart. One such overriding response in the pathogenesis of oxidative stress in multiple tissues relates to intracellular Ca^{2+} overloading. This includes elevated cytosolic free $[Ca^{2+}]_i$ and mitochondrial Ca^{2+}, where mitochondria are a major storage site for Ca^{2+} and the most redox-active organelle.[14] An activation of NADPH oxidase and elaboration of superoxide with intracellular Ca^{2+} overloading is mediated by such calcitropic hormones as parathyroid hormone (PTH), angiotensin II, endothelin-1, and catecholamines. The importance of endogenous antioxidant defenses also deserves to be considered. This includes mitochondrial peroxiredoxin and such metalloenzymes as superoxide dismutase (SOD) and glutathione peroxidase, whose activities depend on Zn and Se, respectively.

Both hypertension and CHF represent progressive systemic illnesses[15] whose major features include: (i) the presence of oxidative stress that overwhelms antioxidant defenses provided by Cu/Zn-SOD and Se-glutathione peroxidase, in diverse tissues including the heart; (ii) an immunostimulatory state, where a dyshomeostasis of intracellular $Ca^{2+}$and Mg^{2+} contribute to endothelial and immune cell activation to produce adhesion molecules, chemokines, and proinflammatory cytokines that begets a vasculopathy of coronary, renal, and mesenteric arterioles; and (iii) a wasting of soft tissues, where Zn-dependent inhibition of ubiquitin-proteasome-mediated protein degradation of skeletal muscle is compromised, and ongoing PTH-mediated resorption of bone, eventuate in reduced lean body mass and the wasting syndrome termed cardiac cachexia.

An ongoing structural remodelling of myocardium accompanies this systemic illness. This includes a concentration-dependent oxidative stress-induced loss of cardiomyocytes, initially via apoptotic and ultimately via necrotic death pathways. Its extracellular matrix (ECM), that includes a fibrillar collagen scaffolding, is also involved. In both postmortem and explanted failing human hearts harvested at the time of cardiac transplantation, ECM remodelling has been described in morphological terms as an adverse accumulation of fibrous tissue presenting as a perivascular/interstitial fibrosis, and as microscopic scarring replacing necrotic cardiomyocytes, and where cardiomyocytes, surrounded by fibrous tissue, become atrophic.[16,17] A degradation of the collagenous scaffolding, induced by its proteolytic degradation and mediated by Zn-dependent matrix metalloproteinases, is an important pathogenic feature of the dilated thin-walled myocardium and is associated with muscle fibre slippage.[18–20]

Thus, factors contributing to the causes and consequences of the systemic illness that accompanies hypertension and CHF are simultaneously operative in promoting the heart's ongoing structural remodelling. It is from this molecular perspective the present report has been structured. It will focus on the role of several macro- and micronutrients and their contribution to the adverse structural remodelling of myocardium found in the failing heart associated with hypertensive heart disease and the clinical syndrome of CHF.

3. Macro- and micronutrients and myocardial remodelling

3.1 Calcium dyshomeostasis

Intracellular Ca^{2+} overloading, including cytosolic and mitochondrial, occurs as a pathophysiological response integral to the induction of oxidative stress and the subsequent appearance of cell injury. Such a scenario occurs with ischaemia/reperfusion (I/R) injury, catecholamine-induced cardiomyocyte necrosis, the secondary hyperparathyroidism (SHPT) that accompanies (see *Table 1*) either aldosteronism, chronic renal failure, or high dietary Na^{+}, and the cardiomyopathy that appears in association with Duchenne muscular dystrophy. An altered redox state, where ROS and RNS overwhelm endogenous antioxidant defenses, leads to a concentration-dependent loss of cardiomyocytes. Apoptotic cell death is not accompanied by an inflammatory cell response and fibroblast-related repair and, therefore, a replacement fibrosis, or scarring, does not appear. At higher $[Ca^{2+}]_i$ concentrations, ROS and RNS lead to necrotic cell death, which is followed by invading inflammatory cells and fibroblasts, and consequent replacement fibrosis. Microscopic scarring, in this case, appears at these sites and is left as a footprint of prior necrosis. In the setting where a circulating substance is involved in promoting intracellular Ca^{2+} overloading with oxidative stress and cardiomyocyte necrosis, such as accompanies elevations in plasma PTH or catecholamines, myocardial scarring is present in both the right and left heart.

Table 1 Factors contributing to the appearance of secondary hyperparathyroidism in patients with hypertension or congestive heart failure

Hypovitaminosis D
Reduced dietary Ca^{2+}
Increased dietary Na^{+}
Loop diuretic
Chronic renal failure
Aldosteronism
Hypoalbuminaemia
Hypocalcaemia
Hypomagnesaemia

In aldosteronism, an integral feature of CHF and some forms of hypertension, intracellular Ca^{2+} overloading of diverse tissues occurs invariably and is PTH-mediated. As shown in *Figure 1*, elevations in circulating PTH occur in response to ionized hypocalcaemia and hypomagnesaemia caused by the heightened urinary and faecal excretion of Ca^{2+} and Mg^{2+} that accompanies aldosterone/1% NaCl treatment (ALDOST).[21–27] SHPT is invoked during ALDOST to restore extracellular Ca^{2+} and Mg^{2+} homeostasis through bone resorption,[28] and increased Ca^{2+} resorption from the kidney and gastrointestinal tract. The important role of PTH-mediated intracellular Ca^{2+} overloading is further evidenced by the hypertension, left ventricular hypertrophy, and adverse structural remodelling of myocardium, as well as myocardial and valvular calcification, arrhythmia and abnormal conduction, and altered vasomotor reactivity with vascular remodelling found in primary hyperparathyroidism.[29,30] A high-Na^{+} diet (8%), which suppresses plasma aldosterone levels, is calciuric in rats and man, and like ALDOST it also leads to SHPT with PTH-mediated bone resorption and intracellular Ca^{2+} overloading (*Figure 1*).[27,31,32] Low-renin hypertension is also accompanied by ionized hypocalcaemia, increased plasma PTH with elevations in platelet $[Ca^{2+}]_i$, and a favourable reduction in elevated blood pressure to dietary Ca^{2+} supplement or Ca^{2+} channel blocker.[1,2,33–35]

Oxidative stress is induced in diverse tissues during SHPT and is expressed by increased plasma 8-isoprostane, activation of NADPH oxidase with increased superoxide production, increased tissue levels of 3-nitrotyrosine, a stable product of peroxynitrite, formed by the reaction between short-lived superoxide and nitric oxide, and activation of redox-sensitive nuclear transcription factor (NF)-κB with a proinflammatory gene cascade it encodes.[36–40] PTH receptors are found in various tissues, including heart, skeletal muscle, and immune cells. In the case of lymphocytes and monocytes, a proinflammatory phenotype accompanies the PTH-mediated intracellular Ca^{2+} overloading, and their activation leads to an invasion of the perivascular space of intramyocardial coronary and renal vasculature and mesenteric circulation. The increase in biologically active cytosolic free $[Ca^{2+}]_i$ is coupled with their increased production of H_2O_2 and altered transcriptome.[41,42] Upregulated gene expression in these cells includes antioxidant defenses, adhesion molecules, and proinflammatory chemokines and cytokines. This vasculitis, together with enhanced fibroblast collagen synthesis,[43] leads to perivascular fibrosis. If sustained, the fibrous tissue response extends into the contiguous interstitial space resulting in interstitial fibrosis. Interventions which interfere with this pathophysiological scenario attenuates the appearance of microscopic scarring, and perivascular/interstitial fibrosis of the right and left atria and ventricles.[44] These cardioprotective measures include: cotreatment with spironolactone, an aldosterone receptor antagonist, that prevents the increased urinary and faecal losses of Ca^{2+} and Mg^{2+} [21,39,45]; parathyroidectomy performed prior to initiating ALDOST;[46,47] cotreatment with either a calcium channel blocker or an exogenous antioxidant, or with an inhibitor of NADPH oxidase or an SOD mimetic.[39,48–51]

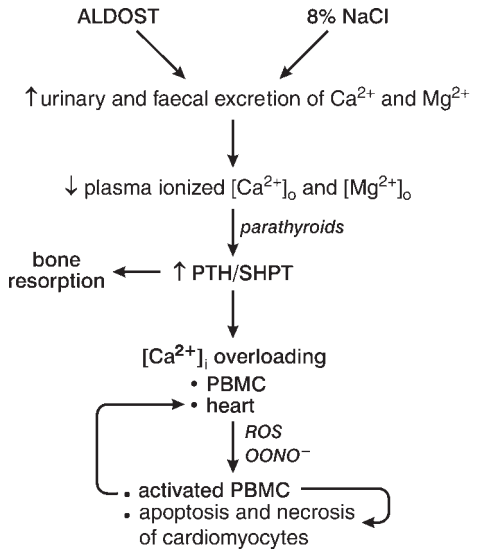

Figure 1 In aldosteronism (ALDOST), where plasma aldosterone levels are inappropriately elevated relative to dietary Na^{+} intake, marked excretory losses of Ca^{2+} and Mg^{2+} lead to a fall in their plasma ionized concentrations. Reduced $[Ca^{2+}]_o$ and $[Mg^{2+}]_o$ are, respectively, major and minor stimuli to the parathyroid glands' secretion of parathyroid hormone (PTH), with secondary hyperparathyroidism (SHPT) accounting for bone resorption in an attempt to restore the homeostasis of these divalent cations. In what is coined as a calcium paradox, elevations in plasma PTH promote intracellular Ca^{2+} overloading and induction of oxidative stress. Reactive oxygen species (ROS) and peroxynitrite ($OONO^{-}$) contribute to intracellular signalling that, in a concentration-dependent manner, eventuates in cell activation (e.g. peripheral blood mononuclear cells, PBMC) and the expression of apoptotic and necrotic cell death pathways in cardiomyocytes. Urinary and faecal losses of Zn are likewise increased during ALDOST (data not shown). A high (8%) Na^{+} diet, which suppresses plasma aldosterone levels, also leads to SHPT because of increased excretory losses of Ca^{2+}.

Thus, Ca^{2+} dyshomeostasis, together with PTH-mediated intracellular Ca^{2+} overloading and induction of oxidative stress, is integral to the adverse structural remodelling of myocardium that includes cardiomyocyte necrosis with scarring and appearance of an immunostimulatory state leading to vasculitis, and ultimately, a perivascular fibrosis of the intramural coronary circulation extending into the contiguous interstitial space. Iterations in Ca^{2+} balance, however, rarely occur in isolation. Mg^{2+} is a natural antagonist to intracellular Ca^{2+} entry through L-type Ca^{2+} channels and mitochondrial permeability transition pore.[52] The contribution of hypomagnesaemia to cardiac remodelling has been studied in rodents using a Mg^{2+}-deficient diet.

3.2 Magnesium dyshomeostasis

Hypomagnesaemia occurs in patients with diabetes, metabolic syndrome, alcoholism, HIV, those receiving Mg-wasting drugs, and critically ill cancer patients.[53] Hypomagnesaemia has been reported in 63% of intensive care patients and up to 45% of patients with acute myocardial infarction and is associated with increased mortality.[54] Hereditary hypomagnesaemia can cause a progressive dilated cardiomyopathy and heart failure.[55]

Severe dietary deficiency of Mg^{2+} (MgD) in animal models causes myocardial necrosis, neuromuscular hyperexcitability, arrhythmias, increased oxidative stress, and enhanced myocardial susceptibility to I/R stress.[56] Circulating levels of proinflammatory neuropeptides, substance P (SP), and calcitonin gene-related peptide are increased in MgD due to their release from sensory-motor neurons (*Figure 2*). These neuropeptides may trigger inflammatory/oxidative events which promote cardiomyopathy.[57] Increases in

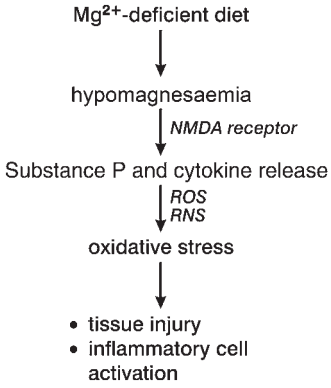

Figure 2 Dietary Mg^{2+} deficiency is accompanied by hypomagnesaemia and release of substance P and cytokines, with ROS and RNS generation leading to oxidative stress, subsequent tissue injury, and inflammatory cell activation.

PGE_2, circulating histamine, and hypersensitivity to applied catecholamine stress also occur. Importantly, elevations of plasma SP preceded that of nitric oxide (NO) in severe MgD rats and this was concurrent with an indicator of systemic oxidative stress, red blood cell glutathione (GSH) loss.[58] L-NAME treatment attenuated this GSH depletion, suggesting a prooxidant role for NO during MgD. The *N*-methyl-D-aspartate (NMDA) receptor complex is an important mediator of neuropeptide release and this receptor is blocked by Mg^{2+} in a voltage-dependent manner. Pretreatment of MgD rats with MK-801, an NMDA receptor blocker, prevented SP loss from dorsal root ganglia[59] and myocardial ICAM expression was decreased along with CD11b-positive inflammatory cells.[59] SP also alters the functional state of endothelial cells, mast cells, macrophages, polymorphonuclear leukocytes (PMNs), and T-lymphocytes. MgD resulted in the elevation of T-cell-derived IFN-γ which was blocked by an SP receptor (NK-1) antagonist and MgD increased the number of circulating PMNs, which displayed significant increases (up to 10-fold) in basal superoxide production indicating systemic oxidative stress; SP receptor blockade also attenuated endogenous PMN activation to reduce superoxide generation.[60,61]

The gut is also rich in neuropeptides, and during MgD severe mucosal inflammation occurs with pronounced PMN infiltration along with enhanced gut permeability that may release endotoxin or lipopolysaccharide (LPS) into circulation.[62] LPS alone induces systemic elevations of TNF-α, IL-1α, and IL-6, which mediate chronic cardiac dysfunction, and it can also stimulate TNF-α production by adult rat cardiomyocytes by activating LPS receptors (CD14),[63] which are upregulated in MgD cardiac tissue.[64] Thus, the substantial increases in plasma TNF-α, IL-1, and IL-6 in MgD rats are due, in part, to SP-mediated gut permeability that increases circulating LPS. SP receptor blockade in MgD rats significantly lowers plasma TNF-α levels in plasma and cardiac tissue,[57] implicating a combined SP and LPS-mediated proinflammatory cascade. TNF-α may be elevated in chronic heart failure along with IL-6. Cardiac-specific overexpression of TNF-α resulted in a heart failure phenotype in mice that exhibited left ventricular dysfunction and cardiac remodelling.[65] TNF-α is a major contributor to the cardiomyopathy of MgD since it was markedly elevated in both the plasma and myocardial lesions after only 3 weeks of MgD.[66]

Thus, both a blockade of SP release from neural tissue and inhibition of the SP receptor significantly reduce the pro-inflammatory state in the hearts of MgD animals. The pro-oxidant elevations of free radicals in the I/R rat heart were also inhibited by pretreatment with SP receptor blockers. Additional studies with antioxidant drugs also showed cardioprotection, since treatment of MgD rats with sustained-release pellets containing alpha-tocopherol, probucol, D-propranolol (non-beta-blocking form), and epicaptopril (the SH-donor stereoisomer of captopril) significantly reduced focal myocardial lesions.

In summary, SP can produce free radicals directly (superoxide and NO) and indirectly (by stimulating cytokine release). Blockade at each level of this neurogenic inflammatory cascade (the SP receptor, the NMDA receptor, and antioxidant treatment) prevented these prooxidant effects in MgD animals. Overall, these studies of cardiomyopathy due to MgD reveal striking parallels with multiple clinical disorders where hypomagnesaemia is present. Translation of therapies that are effective in these experimental MgD models to clinical applications represent a challenge for future studies.

3.3 Zinc dyshomeostasis

Zinc is an essential micronutrient integral to the activity of various metalloenzymes that include angiotensin-converting enzyme and matrix metalloproteinases.[67,68] Hypozincaemia accompanies bodily injury including acute myocardial infarction.[69–71] Zinc deficiency with hypozincaemia, coupled with an associated impairment in Zn-dependent metalloenzymes, has been reported in the elderly, in patients with hypertension, and in those with CHF having dilated cardiomyopathy.[3–6,8,72–74]

In the case of aldosteronism, a fall in plasma Zn is related to its increased urinary and faecal excretion and to its preferential translocation to sites of injury, including the heart, where it contributes to tissue repair and to antioxidant defenses provided by increased Cu/Zn-SOD activity.[75–77] Further evidence in favour of a Zn deficiency during ALDOST includes: reduced plasma Cu/Zn-SOD activity; a fall in bone Zn that occurs in response to PTH-mediated bone resorption; thymic atrophy; and a failure to gain weight.[75,76]

The translocation of Zn to tissues, where it serves as an antioxidant, is intrinsically coupled to intracellular Ca^{2+} overloading that acts as a prooxidant. The relative preponderance of prooxidant:antioxidant determines the heart's redox state and fate of cardiomyocytes. A Zn supplement in the setting of aldosteronism serves to attenuate scarring in keeping with reduced oxidative stress-induced cardiomyocyte necrosis. It does not prevent coronary vasculitis and subsequent perivascular fibrosis since the associated ionized hypocalcaemia and SHPT are not corrected by $ZnSO_4$ cotreatment.[78] However, Zn supplementation has proved efficacious in preventing a diabetic cardiomyopathy in streptozocin-treated rodents,[79] and is cardioprotective in the Ca^{2+} overloading associated with I/R injury, each of which are not associated with SHPT.[80]

3.4 Selenium dyshomeostasis

Selenium is another essential micronutrient. Relevant to cardiac remodelling, the main selenoproteins are glutathione peroxidase (GSHPx) and thioredoxin reductase.[81]

A Se-deficient diet, as occurs with the consumption of vegetables grown in the Se-poor soil in the Keshan Province of China, is associated with the appearance of a DCM in local children known as Keshan's disease, which is often reversible with Se supplementation.[82] Se deficiency has reappeared in western medicine secondary to gastrointestinal disorders interfering with or contributing to the loss of dietary Se (e.g. Crohn's disease), bariatric surgery for weight reduction, and long-term parenteral nutrition (TPN) devoid of Se. Several cases of life-threatening heart failure and DCM have been reported in patients on home TPN, or after marked weight loss following bariatric surgery.[82] Reductions in serum Se, albeit of uncertain origins, have been found in African-American patients who reside in Memphis, Tennessee, and have a DCM. Tennessee soil is not known to be Se-deficient.[8]

Morphological features of this Se-deficient DCM include a widespread myocytolysis with replacement fibrosis scattered throughout the right and left ventricles and atria.[83–85] In addition, diminished Se concentrations and reduced activities of GSHPx are found in blood, heart, liver, kidney, and skeletal muscle.[83,86] Fuyu[87] has suggested that Keshan's disease is a mitochondrial cardiomyopathy with enlarged, swollen, and dysfunctional mitochondria having reduced oxidative phosphorylation and GSHPx activity, coupled with increased Ca^{2+} content. Furthermore, transgenic mice lacking functional mitochondrial thioredoxin reductase have been shown to develop a fatal form of cardiomyopathy.[88] Further investigation into the role of Se deficiency in the appearance of a DCM is warranted.

3.5 Copper dyshomeostasis

Other micronutrients, such as Cu^{2+} and iron can also contribute to an adverse remodelling of myocardial structure. However, a discussion of the adverse consequences of iron deficiency or iron overload is beyond the scope of this brief review.

In both rodents or pigs, a deficiency of Cu^{2+} has been found to be accompanied by a remodelling of myocardium. This includes the appearance of a dilated, thin-walled cardiomyopathy and even its rupture.[89] At an ultrastructural level, non-aligned myofibrils with disrupted Z bands are accompanied by increased volume density of mitochondria with disarranged cristae.[90–92] A repletion of dietary Cu^{2+} is accompanied by a reversal of these iterations in structure. The role of Cu in regulating the activity of lysyl oxidase, integral to promoting the crosslinking of collagen and elastin, and Cu/Zn-superoxide dismutase, an antioxidant defense mechanism, is thought to contribute to the slippage of muscle fibres, a weakening of myocardium, and unbridled oxidative stress that includes structural–functional impairments of its mitochondria.

3.6 Vitamin D dyshomeostasis

Low vitamin D status affects myocardial structure and function and this relationship has clinical relevance.[11,93,94] Vitamin D_3 deficiency and reduced levels of the active vitamin D metabolite, 1,25-dihydroxyvitamin D_3 ($1,25(OH)_2D_3$) have been associated with the aetiology and pathogenesis of CHF.[11] More recently a study of 18 225 men enrolled in the Health Professionals Follow-Up Study reported that men with low vitamin D status had 2.5 times the risk of having a myocardial infarction.[95] Zittermann *et al.*[96] have recently reported that low serum calcitriol levels are independently associated with poor clinical outcome in patients with CHF awaiting cardiac transplantation. In these patients, whose lifestyle is often constrained to housebound because of symptomatic heart failure, marked reductions in plasma 25(OH)D levels are often present, together with elevations in serum PTH in keeping with SHPT.[97,98] In the absence of sunlight therapy, addressing the optimal intake of vitamin D to correct the profound levels of vitamin D deficiency found in these patients becomes a major challenge.[99]

Prior to these clinical observations, studies from the Simpson lab demonstrated that vitamin D_3 deficiency alters myocardial function, morphology, and ECM.[100–102] Recently, it was shown that ablation of the vitamin D receptor (VDR) signalling system results in profound changes in heart structure[103] and that the VDR knockout (VDRKO) mouse phenotype is characterized by cardiac hypertrophy and fibrosis with increased interstitial collagen deposition.[104] Animal studies have revealed that $1,25(OH)_2D_3$ affects two processes central to cardiomyocyte function. First, $1,25(OH)_2D_3$ was shown to alter Ca^{2+} handling resulting in increased sensitivity of heart to contractile stimuli, and second it influences remodelling of heart and increases heart size and collagen content.[11,93,103–105]

Analysis of the promoter region of the collagen-I (COL1A1) gene shows sequence homology to a VDR responsive element.[105,106] Moreover, matrix metalloproteinase-13 (MMP-13) has been shown to be transcriptionally upregulated by $1,25(OH)_2D_3$ in osteoblasts.[107] Thus, vitamin D status has been linked to the regulation of ECM formation, turnover, and integrity in target tissues, including heart. Fibrosis is a classic feature of cardiac hypertrophy characterized by the turnover of ECM and the accumulation of collagen, particularly, collagen type I.[108] The collagen content of the heart is determined by a balance between the synthesis and degradation of collagen, which has been shown to be consistently increased in the models of heart disease.[109] MMPs and tissue inhibitors of metalloproteinases (TIMPs) contribute to tissue remodelling in a number of disease states, including heart disease. ADAMTS-1, like MMP-2, possesses gelatinolytic activity, thus degrades type I collagen.[110] A recent report showed greater accumulation of total collagen, fibrosis, and COL1A1 protein levels in the hypertrophic hearts of VDRKO mice.[104] This observation was interpreted as being a result of VDR ablation affecting COL1A1 stability through an alteration of MMP, TIMP, and ADAMTS expression in heart and associated cells. It has been shown that MMPs have a predominant role in hydrolyzing ECM proteins and these enzymes have been proposed to mediate collagen degradation leading to left ventricular dilation, and ultimately to CHF.[111] The complex nature of heart failure-related remodelling has been addressed in recent studies showing that caveolin-1 null-mutant mice have increased MMP-2 activity,[112] and angiotensin-converting enzyme inhibitors reduce MMP-2 activity.[113] Furthermore, left ventricular hypertrophy has been associated with increased MMP-2 activity, and its transition to heart failure with increased TIMP-2 levels and collagen deposition.[114]

In an effort to better understand VDR's role in ventricular remodelling and fibrosis, microarray and real-time RT–PCR were used to identify possible ECM genes that are

differentially expressed in VDRKO mice (unpublished observations). Subsequently, levels of the identified ECM gene products were analysed by immunoblotting. In these studies, it was found that hypertrophic VDRKO hearts had increased MMP-2 expression at both the transcriptional and translational levels. Increased TIMP-2 mRNA and protein expression, with a concomitant decrease in TIMP-1 and TIMP-3 gene expression in the hearts of female VDRKO mice relative to the WT mice, was also observed. Moreover, there was a significant increase in VDRKO/WT ratio for TIMP-2 protein expression in female mice when compared with the male VDRKO mice, indicative of a lesser degree of heart remodelling in females. This approach ultimately revealed that a member of ADAMTS subfamily, ADAMTS-1, is upregulated both at transcriptional and protein levels in VDRKO mice when compared with control wild type (WT) mice. Overall, it was observed that expression of ADAMTS, collagen, MMP, and TIMP forms are regulated in the cascade of events leading to ventricular remodelling *in vivo* in the VDRKO mouse.

Studies have shown a relationship between the robust increase in TIMPs and degree of left ventricular hypertrophy in patients with heart failure.[115] It has been reported that TIMP-1 and TIMP-2 form a complex with MMP-1 and MMP-2, respectively.[116] However, the modulation of TIMPs expression was reported to be independent of MMP expression.[117] It has been shown that the ratios, specifically of TIMP-2/MMP-2, were significantly increased in the left ventricular remodelling, and suggest that upregulation of TIMP-2 expression might be independent of MMP-2 expression in ventricular remodelling, and ultimately cardiac hypertrophy. Studies suggest that the observed decrease in remodelling in female mice involves an increased relative expression of TIMP-2 in female VDRKO vs. WT mice, in contrast to the increase in male VDRKO TIMP-2 levels. The mechanism of regulation of TIMP-2 at present is unclear. However, a transcriptional action of vitamin D on TIMP-2 expression is supported by the presence of an AP-1 element in the promoter of its gene.[118] Cardiomyocyte Ca^{2+} handling and contraction requires PKC activation, and thus PKC activity could modulate transcriptional regulation of such AP-1 elements.[119]

Increased MMP-2 activity is found in the fibrotic hearts of the VDRKO mice when compared with WT mice.[104] The increase in MMP-2 activity, and its expression in the VDRKO mice, may be induced by the alterations in the myocardial environment that take place in response to hypertrophic stimuli, such as lack of cardiac VDR signalling and/or release of inflammatory mediators. An increase in MMP-2 protein expression, with concomitant increase of TIMP-2, is associated with the enhanced COL1A1 levels and fibrosis and cardiac hypertrophy in VDRKO mice. TIMPs bind to the active site of MMP, blocking their access for degradation of collagen substrates.[119] In addition, ADAMTS-1 is partially inhibited by TIMP-2 and TIMP-3.[120,121]

Thus, vitamin D levels play an important role in maintaining myocardial viability and ECM integrity by regulating the dynamics (activity, production, and expression) between MMPs, ADAMTSs, and TIMPs in heart remodelling. These findings demonstrate a collective role for ADAMTS-1, COL1A1, MMP-2, and its endogenous inhibitors (TIMPs) in the cardiac hypertrophy and fibrosis that accompanies vitamin D deficiency[101,102] and VDR ablation.[104]

4. Summary and conclusions

The heart's failure as a muscular pump has its origins rooted in an adverse structural, biochemical, and molecular remodelling of myocardium that includes its cardiomyocytes, ECM, and intramural coronary vasculature. The ongoing nature of such remodelling contributes to the progressive nature of heart failure.

Contributory to such pathological remodelling, irrespective of the aetiological origins of heart failure, is a dyshomeostasis of such macro- and micronutrients as Ca^{2+}, Mg^{2+}, Zn^{2+}, Se^{2+}, and vitamin D, which are predominantly derived from external sources and often inextricably dependent on one another (e.g. hypovitaminosis D begets SHPT with PTH-mediated $[Ca^{2+}]_i$ overloading). Insufficient dietary intake, inadequate sunlight exposure, excessive excretory losses, and/or a preferential translocation of cations from the intravascular compartment to injured tissues, where they contribute to wound healing, lead to disturbances in their homeostasis. The resulting nutrient imbalance is the basis for a common pathophysiological response, i.e. the induction of oxidative stress. ROS and RNS overwhelm endogenous antioxidant defenses, and lead to untoward intracellular signalling that accounts for reduced cardiomyocyte survival, an immunostimulatory state with activated inflammatory cells contributing to a proinflammatory vascular phenotype, and the appearance of fibrous tissue (or fibrosis). The replacement of any one of these nutrients alone will not suffice and would not prove to be completely cardioprotective. Polynutrient supplements are therefore essential to correct the dyshomeostasis of these interconnected nutrients and to prevent adverse myocardial remodelling.

An improved understanding of how these macro- and micronutrients account for the causes and consequences of adverse myocardial remodelling carries with it the potential of identifying new biomarkers predictive of risk, onset and progression, and response to intervention(s), which can be monitored non-invasively and serially over time. Moreover, such incremental knowledge will serve as the underpinning to the development of novel strategies aimed at preventing and/or regressing the ongoing adverse remodelling of myocardium. The time is at hand and propitious to recognize the importance of macro- and micronutrient dyshomeostasis in the evaluation of hypertension and CHF.

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