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Over-nutrition and Metabolic Cardiomyopathy

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Abstract

Cardiovascular disease, which accounts for the highest morbidity and mortality in the United States, has several major risk factors, including aging and diabetes. Overweight and obesity, especially abdominal obesity, have been increasingly implicated as independent risk factors in the development of cardiovascular disease. Metabolic and/or diabetic cardiomyopathy has been especially associated with excess body weight caused by chronic over-nutrition and high-fat feeding. In the initial stages, obesity is now understood to cause significant dysregulation of cardiac fatty acid and glucose metabolism. These abnormalities are due, in part, to increased oxidative stress, which in turn can cause deleterious effects on intracellular signaling pathways that control cellular growth and proliferation. This increase in oxidative stress is coupled with reduced anti-oxidant species and dysregulation of metabolic signaling pathways. The cardiomyopathy seen with obesity is associated with increased interstitial fibrosis and diastolic dysfunction. Over time, evolving abnormalities include hypertrophy and systolic dysfunction, eventually leading to heart failure.

Keywords

insulin; metabolic; signaling; heart

1. Introduction

Obesity caused by excess feeding (over-nutrition) has become a problem of epidemic proportions and is the underlying cause of many different metabolic disorders and chronic diseases such as diabetes and cardiovascular disease (CVD) (1–3). Obesity induced by high-

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fat and high carbohydrate intake is a major risk factor for the development of heart disease (4–6). Individuals who are obese or have excess body weight carry a higher overall lifetime risk of developing diabetes and cardiovascular diseases (2, 5–7). Even though CVD is the highest cause of mortality in diabetic patients, the incidence of development of diabetic cardiomyopathy in these patients independent of other co-morbid risk factors has not been fully elucidated (8). In such patients, diet control and exercise have been shown to improve morbidity and function, and even reverse some of the pathophysiological effects of over-nutrition (1, 9). As such, many prophylactic strategies are correctly geared towards the reduction or elimination of risk factors predisposing to CVD or type-2 diabetes mellitus (T2DM), which seek to correct the underlying metabolic abnormalities leading to the pathologic state. In addition to its well-known role in promoting hypertension, diabetes and CVD, over-nutrition also promotes impaired cardiac, as well as skeletal muscle insulin metabolic signaling (6, 10–11). This brief review summarizes our contemporary understanding of how over-nutrition contributes to this impaired metabolic signaling and associated myocardial maladaptive structural and functional changes.

2. The Cardiorenal Metabolic Syndrome

Over-nutrition is commonly defined as chronic consumption of a diet consisting of 60% fat and 20% fructose, which closely mimics the prevailing diet constitution in the western society today (the “Western” diet) (1–3, 5, 9). Even so, individual components of over-nutritious diet have differing health outcomes due to their effects on gene transcription and metabolic signaling pathways (2, 5–6). Obesity induced by high-fat feeding is a major risk factor for the development of heart disease (5, 12–14). In addition to its well-known role in promoting atherosclerosis and hypertension, over-nutrition has also been shown to cause impaired cardiac metabolism in the early stages due to its ability to induce oxidative stress in the cardiomyocyte (15). In recent years, a lot of attention has been focused on the cardiorenal metabolic syndrome as a pre-existing condition to the development of diabetes and cardiovascular disease (16). The cardiorenal metabolic syndrome can be summarized as a loosely defined group of risk factors, such as insulin resistance, dyslipidemia, high blood pressure and the main feature of central or abdominal obesity, that predispose to well-characterized medical conditions such as diabetes and cardiovascular disease (16, 17). The central feature of abdominal obesity may predispose to the development of the other characteristics of the cardiorenal metabolic syndrome, which may develop later (16–18). Thus, the cardiorenal metabolic syndrome may exist for many years before clinical problems develop, and in addition to factors related to the deteriorating medical condition, may be susceptible to chronic oxidative stress caused by obesity-related pathophysiologic changes in the cardiovascular system and overall metabolism of the body, in regards to its progression to full-blown disease.

3. Impaired cardiac insulin metabolic signaling and associated cardiac dysfunction

Excess nutrients in the form of fat and carbohydrates promote insulin resistance in cardiovascular tissue as well as conventionally insulin-responsive tissue such as muscle, fat and liver (2,5,11). In addition to over-nutrition, several other mechanisms, such as enhanced activation of the renin-angiotensin-aldosterone system (RAAS), inflammation and oxidative stress further antagonize insulin metabolic signaling (10–11, 18). Angiotensin II (Ang II) and aldosterone increase the generation of reactive oxygen species (ROS) in various tissues including the myocardium (11,19). There is emerging evidence that over-nutrition, Ang II and aldosterone promote insulin resistance through activation of the mammalian target of rapamycin (mTOR)/S6 kinase 1 (S6K1) signaling pathway (2,11–13, 20, 21). The activated/phosphorylated S6K1, in turn, causes increased serine phosphorylation of insulin receptor

substrate 1 (IRS-1), leading to its degradation and/or downstream inhibition of the engagement with phosphatidylinositol 3 kinase (PI3K) (11–13, 20, 21). This action leads to decreased protein kinase B (Akt) activation/downstream insulin signaling and to reduced myocardial and skeletal muscle glucose uptake, impaired nitric oxide (NO) production in endothelial cells, and reduced myocardial glycogen synthase activity and generation of ATP (20–25). Insulin resistance and dysregulated mitochondrial fatty acid oxidation causes increased myocardial accumulation of fatty acids and reduced myocardial glucose and fatty acid utilization (Fig 1) (2,11).

Insulin receptor substrate (IRS-1) is thought to be a convergence point for the insulin signaling pathway. Serine phosphorylation on multiple IRS-1 residues reduces its tyrosine phosphorylation and downstream metabolic signaling. Although, multiple kinases are known to serine-phosphorylate IRS-1, the mTOR/S6K1 pathway is especially important in nutrient and stress-mediated IRS-1 serine phosphorylation (11–13, 20). The beneficial effects of insulin on the heart are mediated by the IRS-1/PI3K/Akt signaling pathway which promotes myocardial glucose uptake, NO mediated blood flow, and diastolic relaxation. Accordingly, cross-talk between the metabolic and hemodynamic actions occurs as a result of insulin metabolic signaling in the heart (21–23). Over-nutrition and excess RAAS activation are increasingly recognized to have an interactive action on the stimulation of mTOR/S6K1 signaling, which, in turn, attenuates insulin metabolic signaling in cardiovascular tissues (5,11). Recent work from our laboratory indicates that Ang II activates S6K1 in heart and vascular tissue and leads to diminished insulin metabolic signaling and biological consequences, such as impaired NO-mediated vascular relaxation and impaired myocardial glucose utilization and diastolic relaxation (11).

Phosphorylation of S6K1 by mTOR in the heart is mediated by the mTOR complex 1 (mTORC1), which is sensitive to rapamycin. Cardiac overexpression of mTOR protects against cardiac dysfunction following left ventricular (LV) pressure overload. Further, ablation of raptor, the scaffolding protein that mediates mTORC1 formation and mTOR substrate activation, results in impairment of adaptive hypertrophy and causes heart failure in mice (2,11). These observations suggest that mTORC1 activation in certain circumstances may have a cardio-protective effect, and underscore the need for a better understanding of mTOR-mediated signaling in cardiac pathology. We have shown that cardiac mTOR is activated in insulin resistant Zucker obese rats but is not activated in heart tissues of Zucker diabetic fatty rats. It is conceivable that the lack of activation of mTOR in cardiac tissue under conditions of obesity-induced diabetes may be a metabolic switch associated with insulin deficiency and more advanced diabetic cardiomyopathy (11). Recent studies from our group have also begun to unveil cross-talk between RAAS and mTORC1 mediated by the angiotensin type-2 receptor (AT2R), and therefore the possible existence of an adaptive beneficial mTOR-AT2R signaling loop.

4. Dysregulation of cardiac fatty acid and glucose metabolism

The normal heart derives most of its energy from mitochondrial fatty acid metabolism, with only about 30% of its energy coming from glucose oxidation (26). During insulin resistance and diabetes, the rate of glucose uptake is reduced while that of circulating free fatty acids is increased; leading the heart to utilize even more fatty acids for its energy needs (14, 22). Excess levels of insulin in the coronary perfusion also promotes increased uptake of free fatty acids in the heart due to up-regulation of the cluster differentiation protein 36 (CD36), a potent fatty acid transporter (27) (Fig 1). In fact, ablation of CD36 has been shown to prevent the induction of metabolic stress and cardiac fat accumulation associated with a high-fat diet, even in the presence of an ischemic component such as artificially induced cardiac overload (22). Even though about twenty percent of FA uptake occurs spontaneously

across the cell membrane and some of it is mediated by other transporters like fatty acid binding protein (pmFABP) or fatty acid translocase (FAT), fatty-acid uptake is mostly dependent on and directly correlates with the amount of CD36 in the sarcolemmal membrane of the cardiomyocyte (28). Both insulin and adenosine monophosphate protein (AMP) kinase can increase plasma membrane CD36 and glucose transporter type 4 (GLUT4) uptake in conjunction with increased ATP requirement and with enhanced insulin metabolic signaling, respectively (14, 22, 23). Different vesicle-associated membrane proteins (VAMPs) are involved in the trafficking of CD36 and GLUT4 (29).

5. Development of metabolic cardiomyopathy

Diabetic cardiomyopathy, first identified by Rubler and colleagues in 1972 (30), is described essentially as a cardiac complication involving reduced cardiac function (initially only diastolic dysfunction) independent of ischemia or hypertension (14). This cardiomyopathy seen in association with over-nutrition and insulin resistance is characterized by increased interstitial fibrosis and impaired LV relaxation which we have characterized by high resolution cine magnetic resonance imaging (Fig 2). Progression of cardiac dysfunction is related to the toxic action of accumulated free fatty acids and impaired mitochondrial biogenesis leading to mitophagy, increased mitochondrial apoptosis and reduced ATP production (31). Accumulation of free fatty acids in the cell (lipotoxicity) finally results in decreased ATP production and decreased cardiac efficiency (8, 11, 14). With progression of the metabolic disease, there are increasing degrees of both diastolic and systolic dysfunction (15, 32). The development of subsequent ventricular hypertrophy, coupled with reduced cardiac energetics, facilitates a reverse substrate shift resulting in decreased expression of fatty acid oxidation genes, and the heart switches back to glucose as the more favorable substrate due to lower energy cost (33–35). Accordingly fatty acid metabolism was shown to be reduced in viral myopathy in mouse heart, similar to an advanced stage of diabetic cardiomyopathy (32, 35, 36). Thus, the increased cellular oxidative stress may eventually lead to reduced fatty acid uptake and utilization. Indeed, during advanced stages of cardiomyopathy, multiple factors are thought to be contributing to inhibition of fatty acid metabolism, such as reduced expression of the peroxisome proliferator activated receptor (PPAR) group of proteins, most notably PPAR-alpha, which, among other things, are involved in direct transcriptional regulation of fatty acid metabolism genes, the toxic effect of accumulated free fatty acids on mitochondrial biogenesis and lipoapoptosis, among other factors (8, 34, 37). Because of these effects, oxidative stress eventually precipitates impaired fatty acid oxidation and utilization, resulting in further accumulation of fatty acids, thus forming a vicious loop, which has been implicated as an underlying cause of disordered cardiac metabolism and associated myocardial structural and functional alterations (8, 15, 38, 39). Also, since the heart normally derives most of its energy from fatty acid oxidation, the above changes result in reduced ATP yield which cannot match the heart needs; precipitating impaired cardiac contractility and diminished ejection fraction, and setting up the next stage in the progression of the disorder towards systolic dysfunction and eventual heart failure (32).

In addition, over-nutrition and the associated insulin-resistant state leads to over-activation of cardiac RAAS (18) which, in turn, contributes to the increased NADPH oxidase activity and increased cytosolic ROS production, reduced bioavailable NO, impaired insulin metabolic signaling and diastolic dysfunction (10, 18) (Fig 2). Oxidative stress is exacerbated further by the toxic effect of ROS molecules such as superoxide, hydrogen peroxide and peroxynitrite thereby deteriorating mitochondrial function further (40,41). Thus, a complex interplay between ROS derived from mitochondrial and cytosolic sources acts to exacerbate mitochondrial dysfunction. These metabolic abnormalities further impair

cardiac contractility additionally contributing to the worsening systolic dysfunction and leading to heart failure.

6. Endoplasmic reticulum stress

In addition to the direct toxic effects caused by oxidative stress, excessive ROS also has deleterious effects on the endoplasmic reticulum (ER) and causes impairment of protein folding and other post-translational modifications occurring in rough ER (24). Since the ER is a primary site for synthesis and folding of many membrane-bound and secreted proteins, accumulation of mis-folded proteins as a result of membrane destabilization in the ER lumen of ensuing ER stress. This ER stress leads to a compensatory response termed the unfolded protein response (UPRE); targeting the degradation of terminally mis-folded proteins by an ER associated degradation mechanism (ERAD) (25). In chronic over-nutrition conditions leading to obesity, there is a mismatch between the physiological UPRE and protein translation due to increased nutrient intake, causing further membrane destabilization and ER stress. This leads to a release of calcium further enhancing mitochondrial oxidative stress and ultimately causing mitochondrial apoptosis and mitophagy. To this point, infusion of the fatty acid palmitate causes initial compensation response, but later resulted in compromised ER membrane integrity and severe ER stress, as evidenced by the leakage of ER-associated chaperones into the cytosol within only a few hours of the infusion. In addition, the ER stress also further increases fatty acid accumulation/lipotoxicity by indirectly increasing lipogenesis via the sterol regulatory element binding protein 1c (SREBP1c) (18, 19, 42). ER stress also worsens insulin resistance directly through activation of the redox-dependent serine kinases such as Jun amino-terminal kinases (JNK), which serine phosphorylate IRS-1 and decreases downstream insulin-signaling (24, 25).

7. Summary

In summary, chronic over-nutrition can cause cardiac insulin resistance, activation of the tissue RAAS, mitochondrial uncoupling and later on reduced fatty acid metabolism and enhanced oxidative stress and ER stress in the heart (8, 42–44). These lead to structural and functional changes initially characterized by impaired diastolic relaxation which can progress to heart failure. Further characterization and elucidation of the etiological factors leading up to this condition and the pathogenic features of metabolic cardiomyopathy, may help to improve the morbidity and mortality associated with the development of heart disease in conditions of over-nutrition and diabetes.

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Abbreviations

CVD	cardiovascular disease
RAAS	renin-angiotensin-aldosterone system
Ang II	angiotensin II
ROS	reactive oxygen species
mTOR	mammalian target of rapamycin

S6K1	S6 kinase 1
IRS-1	insulin receptor substrate
PI3K	phosphatidyl-inositol 3 kinase
Akt	protein kinase B
NO	nitric oxide
mTORC1	mTOR complex 1
AT2R	angiotensin type 2 receptor
CD36	cluster differentiation protein 36
LV	left ventricular
AMP	adenosine monophosphate protein
GLUT4	glucose transporter type 4
ER	endoplasmic reticulum
UPRE	unfolded protein response
ERAD	endoplasmic reticulum associated degradation
SREBP1c	sterol regulatory element binding protein
1c JNK	Jun amino-terminal kinases

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Figure 1.

Impact of over-nutrition mediated by insulin resistance on development of cellular oxidative stress and subsequent metabolic cardiomyopathy in the heart.

Figure 2.
Cine-MRI assessment of Zucker Lean (ZL) vs. Zucker Obese (ZO) rat hearts shows early diastolic dysfunction in the ZO heart.