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I have always thought that the phrase, “eat your heart out,” was an odd expression as it is used most commonly to taunt a competitor. The origins of this phrase are contentious and there are at least three different etymologies. To these three, this issue of our journal adds a dysmorphic fourth.

The focus of this issue is the effect of diet on the cardiovascular system. This effect can either be direct, through food constituents entering our bloodstream, or indirect. Indirect effects are quite hard to envisage until you delve into the article by Max Nieuwdorp. This article highlights the massive fauna of bacteria that live in our gastrointestinal tract and how they can profoundly influence the efficiency with which we extract calories from our diet. The fauna, or microbiota, also synthesize molecules that trigger very specific signaling pathways that regulate metabolism. The article is not for the faint-hearted since it will change your view of coprophagia and fecal transplantation! The description of the underlying biology, and of the clinical findings, is compelling. Furthermore, this topic affects the interpretation of the other articles in this issue that predominantly focus their explanations on the direct effects of diet. I, therefore, suggest it is worth reading Max Nieuwdorp’s review first, since it offers holistic insight to the complex issue of dietary manipulation.

We are fortunate to have the article by Ramon Estruch, the lead author and coordinator of the PREDIMED study (PREvención con Dieta MEDiterránea). This landmark dietary intervention study showed that a Mediterranean diet supplemented with fat, in the form of extra virgin olive oil or tree nuts, significantly reduced events as measured by a composite of hard cardiovascular end points (MI, stroke, or CV death). This was a primary prevention study in an easily identifiable at risk group (men >55 years or women >60 years, with either type 2 diabetes mellitus or at least three of the following: smoking, hypertension, LDL >160 mg/dL, HDL <40 mg/dL, BMI >25 kg/m², or a family history of premature coronary heart disease). The article contains a table of the diet instructions to wet your appetites. Ramon Estruch and Gemma Chiva-Blanch highlight that the exact component of the diet responsible for the salutary effect is not known. However, this knowledge is not necessary since it should be used as part of a lifestyle package in combination with reductions in dietary salt and regular exercise. This advice sounds like “motherhood and apple pie,” but as you will see from their table, commercial bakery products were discouraged.

The likely contents of commercial bakery products and other industrialized aspects of our diet are highlighted by Thomas Sanders. The refresher corner article looks at our diet from a public health viewpoint and emphasizes the impact of government policy on its constituents. These have been particularly effective at driving reductions in the consumption of salt and saturated and/or trans fatty acids, at least in the UK. It is clear from this article that public policy can curb dietary components thought to be harmful and supplement those thought to be beneficial, but it is much more difficult to mandate the form of food, such as fruit and the PREDIMED diet.

While “motherhood and apple pie”-style advice is directly applicable to individuals and can be enshrined in a policy to influence a population, it does not reveal the mechanism responsible for the benefit. Ultimately, this needs to be known in order to identify a therapeutic target amenable to direct and specific manipulation. The article by Manlio Vinciguerra discusses how such targets (eg, Insulin-like growth factor-1, Fibroblast growth factor-21, Sirtuins, and PPARα) were revealed after caloric restriction or from the study of metabolic changes at birth. The switch from the hypoxic environment of the uterus to the oxygen and fat (maternal milk)-rich environment of the neonate is of particular interest. The premise being
that the diseased heart is reverting to a more primitive/fetal phenotype, more dependent on glucose and less dependent on fat. We are reminded that this scenario is also impacted by profound alterations in gut microbiota at birth, which is, in part, contributed to by the ingestion of meconium, as discussed by Max Nieuwdorp. Time will tell if these fundamental signaling processes can be harnessed to slow the aging process and its detrimental effects on heart muscle.

In the morbidly obese, dietary restriction is challenging. In such patients, bariatric surgery can bring the benefits of caloric restriction, which is highlighted by Manlio Vinciguerra despite patient’s satiety. The case report by Rahul Mukherjee emphasizes the systemic benefit of profound weight loss on whole-body metabolism and markers of cardiovascular risk, essentially completely reversing the metabolic syndrome. In contrast, the hot topics article by Oliver Rider discusses the changes that occur within the heart following bariatric surgery. Oliver Rider also highlights the dilemma posed by the obesity paradox, where overweight patients with heart failure tend to do better than their thinner counterparts. These are complex issues with multiple confounders.

The focus on trimetazidine article has been written by Roberto Ferrari and provides a succinct overview of cardiac metabolism and how dietary substrates are turned into high energy phosphate. On this backdrop, actions of trimetazidine are explained in terms of improved efficiency and reduced oxygen requirement.

Finally, Ronak Rajani provides a fascinating article that discusses the detection of fat at various locations within the heart. One that seems to have a particular prognostic relevance is the epicardium. Epicardial adipose tissue (EAT) shows wide inter-individual variation and even within an individual, it is dynamically regulated, and regresses markedly with weight loss following bariatric surgery. Given its prognostic importance, and the overwhelming evidence of diet’s influence, it is definitely time to “EAT out your heart!”

REFERENCES

Nutrient signaling and cardiovascular aging

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Abstract

Aging is a major factor contributing to changes observed in the cardiovascular system in the elderly such as stiffening of the arterial tree and left ventricular diastolic function. These age-related changes in cardiovascular function lower the threshold at which cardiac diseases manifest. Evolutionarily conserved signals triggered by growth and hormones, e.g., insulin and insulin-like growth factors, in response to the intake of specific macronutrients (proteins, carbohydrates, or fats), accelerate aging and mortality in animal models and humans. Dietary restriction, a ~25% reduction in calorie intake while maintaining micronutrients, by reducing the levels of aging-associated growth factors and hormones protects against cardiovascular diseases and against the decline in autonomic function. However, the role of nutrients and nutrient-associated-signaling pathways in the decline in cardiac function and in the increase in cardiovascular diseases during aging is not completely understood. Here, we review the links between caloric intake, growth/hormonal factors, and intracellular signaling pathways in determining cardiac muscle (dys)function and regeneration during aging. Heart Metab. 2014;63:4–7

Keywords: Aging; cardiac hypertrophy; cardiomyocytes; cardiomyopathy; cell signaling; growth factors; heart; laminin; mice models; nutrients.

The performance of the heart decreases with age, and this decrement in performance is a major risk factor for cardiovascular disease and mortality in the human population. However, the molecular pathways underlying cardiac aging are just beginning to be understood. In fact, aging results in a progressive functional and structural decline in the heart and arterial system. Age-dependent cardiac and vascular changes include cardiomyopathy,¹ impaired endothelial function and proliferation, increased stiffness of the arteries,² ³ left ventricular diastolic dysfunction, concentric hypertrophy, decreased systolic reverse,⁴ ⁵ and diminished heart rate variability.⁶ Moreover, as a consequence of the aging process, the interaction between the heart and arterial system adapts to preserve ventricle-arterial homeostasis. Hence, the age-associated structural and functional deterioration due to the intrinsic effects of aging on the myocardium together with the compensatory reactive cardiac modifications in response to the progressive increase of systolic load induced by elevated arterial stiffness, can have a detrimental effect on the aged heart. The view of the heart as a terminally differentiated postmitotic organ (Figure 1) that is unable to replace its damaged cells is shared by the scientific community and goes back to the 1960s. Recently, a dynamic concept of the heart in which cell
Abbreviations

FGF21: fibroblast growth factor 21; IGF-1: insulin growth factor 1; KO: knockout; PPARs: peroxisome proliferators-activated receptors; SIRT: sirtuins

turnover is a crucial component of homeostasis, aging, and disease has been put forward, although this is a matter of much debate.8,9

Figure 1: Representative microscopic field of the mouse myocardium. The myocardium was stained with an anti-laminin antibody. Nuclei were counterstained in blue. Image taken by A. Planavila and F. Villarroja.

Nutrient signaling and cardiac function

The prevalence of heart diseases, such as cardiac hypertrophy and/or the progressive development of congestive heart failure, increases with age. Compelling evidence implicates the protein deacetylases, sirtuins (SIRTs), to act as metabolic sensors to regulate aging. SIRT proteins appear to link nutrition, caloric restriction, and heart disease.10,11 The adult myocardium uses either fatty acids or glucose oxidation as its main energy source, providing 65% and 30% of the energy, respectively.12 However, in contrast with other tissues, the heart is a ‘promiscuous’ substrate consumer. Thus, it adapts its metabolism depending on the type of substrates that are available in order to maintain the constant pump function. The fetal heart, which functions in a relatively hypoxic environment, derives energy from the catabolism of glucose and lactate. Immediately after birth, when the mammalian diet becomes high in fat, the heart switches to fatty acids for myocardial energy production. Cardiac hypertrophy and the development of heart failure are associated with suppression of fatty acid oxidation and metabolic reversion to increased glucose utilization. This shift in the source of energy from fatty acids to glucose is accompanied by a dramatic decrease in the expression of cardiac genes involved in fatty acid metabolism, which are regulated primarily by the peroxisome proliferator activated receptors (PPARs).13 Therefore, the heart senses nutrient signals through PPARs, which, in fact, control the genes involved in fatty acid metabolism. Moreover, it has been shown that SIRT1 controls fatty acid metabolism through an interaction with the PPARα pathway in the heart and prevents the development of cardiac hypertrophy, thereby linking sirtuins, nutrient signaling, and cardiac function.14 Optimal therapeutic interventions that antagonize aging may reduce the occurrence and mortality of adult heart diseases. Therefore, molecular mechanisms mediating life span extension affect aging of the heart and its resistance to pathological insults. Caloric restriction (25% reduction in caloric intake) increases life span and prevents the development of age-associated changes in several animal models.15 It has been shown that cardiac-specific overexpression of SIRT1 delayed aging and protected against oxidative stress in the heart.10,11 Emerging evidence of the involvement of other sirtuins, namely the mitochondrial sirtuins, SIRT3 and SIRT6, reinforces the importance of this family of age-related controllers of heart function in response to nutrients. Modulation of the activity of sirtuins in the heart may represent a novel cardioprotection strategy against aging and certain types of cardiac stress, such as oxidative stress.

Growth factor signaling and cardiac dysfunction during aging

Among the pathways whose inactivation is believed to mediate part of the protective effects of caloric restriction are the PI3K-AKT, Ras, TOR-S6K pathways, which are regulated by growth factors such as insulin, insulin growth factor 1 (IGF-1), and the fibroblast growth factor (FGF) family.11 Here, as a proof-of-concept of the chief role of growth factor signaling in aging-dependent cardiac dysfunction, we will summarize the impact of IGF-1 and FGF21 overexpression in the heart. IGF-1 acts as an intermediate of several growth hormone (GH) responses and affects multiple signaling cascades, resulting in a potent proliferative signal that blocks apoptosis and
stimulates growth in many different cells and organs. The IGF-1 gene undergoes complex transcriptional and posttranscriptional regulation, generating isoforms that differ in their cardioprotective, cardioaccelerating, and regenerative effects. In animal models, newly characterized molecular cross-talk with other signaling pathways involved in aging-associated damage and diseases such as SIRT1 have been identified. The locally acting miGF-1 isoform, which contains a Class 1 signal peptide and a C-terminal Ea extension peptide, is highly expressed in neonatal tissues and in the adult liver, but decreases during aging in the heart, where it is expressed only transiently in response to local damage.  

Mouse genetics have shown that enhancement of the miGF-1 signaling pathway is highly effective in counteracting tissue decline, possibly through its regenerative properties and its promotion of cell survival and renewal, as demonstrated in senescent skeletal muscle. miGF-1 overexpression is able to improve heart function after injury induced by ligation of the left coronary artery or cardiotoxins. This restoration of cardiac function in miGF-1 transgenic mice after myocardial infarction or cardiotox-ini-city is facilitated by the modulation of inflammatory responses, the secretion of paracrine factors, and by a range of novel systemic effects, which, interestingly, all occur in a SIRT1-dependent manner. The robust responses achieved by the miGF-1 isoform suggest a potential mechanistic basis for therapeutic strategies to improve outcomes in age-related heart disease.

FGF21 is a putative mammalian starvation master regulator because it recapitulates the beneficial physiological changes seen in calorie-restricted animals, such as decreased glucose levels, increased insulin sensitivity, and improved lipid profiles. Ectopic overexpression of FGF21 in transgenic mice extends the life span to a similar extent as caloric restriction. FGF21 functions as an endocrine hormone, secreted by the liver, and acts via autocrine mechanisms. Despite its role in nutrient metabolism and aging, there was, until recently, no knowledge about the function of FGF21 in the heart. FGF21 knockout (KO) mice display an increased relative heart weight and develop cardiac dysfunction in response to isoproterenol infusion, indicating eccentric hypertrophy development. This phenotype is accompanied by the induction of cardiac hypertrophy markers and proinflammatory pathways as well as by blocking fatty acid oxidation. These deleterious effects could be reversed by FGF21 treatment in vitro and in vivo. It was also found that FGF21 is secreted by cardiomyocytes, protecting them against hypertrophic insults and is under the transcriptional control of SIRT1. Thus, the heart appears to be a target of systemic and locally generated FGF21, which exerts a protective action.

Conclusions  

Nutrient signaling has a major impact on the way in which the heart ages. Multiple molecular actors (eg, SIRT1, PPARα) sense the type of nutrients and their availability, and subsequent responsive effectors (eg, FGF21, miGF-1) have recently been identified as mediators affecting cardiac homeostasis and aging. These molecules constitute emerging potential targets, which are currently being targeted by several biotech and pharmaceutical companies through nutritional or pharmacological intervention. The ultimate aim of these approaches is to slow cardiac aging and improve human health.

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Does diet alter cardiovascular risk?

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Abstract
Cardiovascular disease continues to be the main cause of morbidity and mortality in the 21st century. The first steps in the prevention and treatment of this disease are to follow a healthy diet and to exercise regularly. The Mediterranean diet has been considered as a model of healthy eating. Several cohort studies and two randomized intervention-feeding trials have concluded that an increase in the adherence to a traditional Mediterranean diet significantly reduces the incidence of cardiovascular events and mortality. An analysis of intermediate markers of vascular risk have shown that the Mediterranean diet improves classical and novel risk factors including blood pressure, lipid profile, lipoprotein particles, insulin sensitivity, and carotid atherosclerosis. Interestingly, the effects of diet on the lowering of blood pressure are independent of salt intake and persist for a long time. These effects have been attributed to the antioxidant, anti-inflammatory, and vasodilatory properties of this diet. However, these protective effects of a traditional Mediterranean diet could potentially be even further enhanced by changing common olive oil to extra-virgin olive oil, increasing the intake of whole grain cereals, nuts, oily fish, and legumes; and, above all, reducing sodium intake. ■ Heart Metab. 2014;63:8–12

Keywords: Atherosclerosis; cardiovascular disease; cardiovascular risk; diet; inflammation; Mediterranean diet; olive oil; polyphenols; salt; vegetables; wine.

Cardiovascular disease (CVD) is the main cause of mortality worldwide and is principally caused by the appearance and progression of atherosclerotic lesions. Atherosclerosis has long been considered as an oxidative disease, which accumulates lipids in the artery wall. However, today it is considered a systemic disease involving low-grade arterial inflammation in which the cell and endothelial expression of adhesion molecules and chemokines participate in the recruitment of circulating leukocytes to the vascular endothelium and migration into subendothelial spaces causing atherosclerotic lesions. Inflammation is characterized by a complex biological cascade of molecular and cellular signals that alter physiological responses. At the site of the injury, cells release molecular signals such as cytokines that cause a number of changes in the affected area, such as dilation of blood vessels, increased blood flow, increased vascular permeability, or exudation of fluids.

Behavioral risk factors are responsible for about 80% of CVD, the most important ones being unhealthy diet, physical inactivity, tobacco use, and excessive use of alcohol. The effects of unhealthy diet and physical inactivity manifest within individuals as increased blood pressure (BP), raised plasma glucose and lipid concentrations, and overweight or obesity. Treatment of these cardiovascular risk factors may delay the progression of atherosclerosis and the appearance of its main clinical manifestations, cardiovascular events, and mortality.
Abbreviations
BP: blood pressure; CVD: cardiovascular disease

The consumption of some key foods (e.g., whole grain cereals, fruits, vegetables, nuts, fish, and a moderate alcohol intake) reduces the risk of cardiovascular disease. However, the Mediterranean diet, as a whole dietary pattern, was ranked as the dietary factor with the highest level of scientific evidence in terms of protection against coronary heart disease.2 Thus, a meta-analysis of cohort studies showed a 10% reduction in fatal and nonfatal cardiovascular events associated with a 2-point increase in a 9-point score of adherence to the traditional Mediterranean diet.3 Nevertheless, the highest level of scientific evidence is only achieved with the performance of randomized clinical trials with “hard” end points as their main outcome. Until now, only two field trials fulfill these criteria, the Lyon Diet Heart Study4 and the PREDIMED trial (PREvencción con Dieta MEDiterránea).5 The first study showed an almost 70% reduction in cardiovascular mortality in subjects with a previous infarction after following a Mediterranean diet, and the PREDIMED trial observed a 30% decrease in cardiovascular events in an asymptomatic high-risk population (Figure 1).

![Fig. 1 Kaplan-Meier estimates of incidence of all major cardiovascular events. All major cardiovascular events: (i) acute myocardial infarction; (ii) stroke; or (iii) cardiovascular death are estimated in the three intervention groups: (i) Mediterranean diet + extra-virgin olive oil (green line); (ii) Mediterranean diet + nuts (red line); and control group (black line). *Hazard ratios stratified by center (Cox model with robust variance estimators). Modified from reference 5. Copyright © 2013 Massachusetts Medical Society. All rights reserved. Abbreviations: CV, cardiovascular; EVOO, extra-virgin olive oil.]

Diet, oxidative stress, inflammation, and atherosclerosis
A Western high-fat high-carbohydrate diet is positively associated with low-grade inflammation, and therefore, contributes to the development and progression of atherosclerosis. The classical Western diet is rich in total fat (and an unbalanced ratio of n-6 to n-3 fatty acids), animal protein, n-6 polyunsaturated fatty acids, and refined sugars, which altogether lead to an increased pro-oxidant and proinflammatory state,6 and may, therefore, be considered as another risk factor for the development of CVD.7 On the other hand, several studies have highlighted that a Mediterranean diet decreases cardiovascular risk in healthy and high-risk populations.8 The Mediterranean diet should be considered as an integrated dietary pattern, not a sum of nutrients. In fact, overall dietary patterns may improve health to a greater extent than isolated foods or nutrients.7 The Mediterranean dietary pattern is characterized by a high content of cereals, fruits, and vegetables (and, therefore, polyphenols), a moderate consumption of olive oil, fish, seafood, nuts, fermented dairy products (yogurt and cheese), poultry, and wine (especially red wine), and a low intake of meat, processed meat, sweets, and industrial bakery products.9 The table enclosed summarizes the main dietary recommendations given to the participants included in the PREDIMED trial (Table 1). The overall quantity of fat intake, and the sources and type of dietary fat, with a special emphasis on α-linolenic acid and oleic acid, and the ratio of n-6 to n-3 fatty acids in this diet, collectively play a crucial role in modulating inflammation, oxidation, and CVD.

The description of the biological mechanisms by which the Mediterranean diet exerts its protective effects adds plausibility to the results obtained in the cohort and clinical trials performed. Several studies have analyzed the effects of the Mediterranean diet on both classical and novel vascular risk factors. In these studies, the Mediterranean diet improved BP, insulin sensitivity, lipid profile, and lipoprotein particle characteristics, without significant changes in body weight or abdominal adiposity. A nonenergy-restricted Mediterranean diet was also very useful in preventing new cases of diabetes and managing metabolic syndromes in high-risk subjects. Scientific evidence has also shown that the Mediterranean diet has a powerful antioxidant and anti-inflammatory effect, both being relevant mechanisms by which this diet decreases the incidence of myocardial infarction, stroke, and cardiovascular mortality.10 The Mediterranean diet also reduces carotid intima-media thickness and may even induce plaque regression as measured by ultrasonography.
These findings that the Mediterranean diet delayed intima-media thickness and, more importantly, delayed plaque progression may explain, at least in part, the reduction in cardiovascular events observed in the Mediterranean diet arms of the PREDIMED trial. Nutrigenomic studies have observed that the Mediterranean diet has a protective effect on the expression of several proatherogenic genes involved in vascular inflammation, foam cell formation, and thrombosis. However, an even healthier Mediterranean dietary pattern may be obtained by changing common olive oil to extra-virgin olive oil, increasing the intake of whole grain cereals, fatty fish, nuts, and legumes, maintaining a moderate consumption of wine, preferably with meals, and, above all, decreasing salt intake.

**Diet and hypertension**

Hypertension is certainly a major risk factor for cardiovascular morbidity and mortality. Indeed, 9.4 million deaths each year (16.5% of all deaths) are attributed to hypertension, accounting for 54% of stroke and 47% of coronary heart disease events.

Excess salt (sodium chloride) intake plays a major role in the pathogenesis of elevated BP and endothelial dysfunction. High dietary salt intake represents a risk factor for the development of CVD by increasing BP and reducing vascular nitric oxide bioavailability, thereby limiting endothelium-dependent dilation. In a recent review, a moderate reduction in salt intake (mean reduction -4.4 g/day) resulted in clinically significant decreases in systolic and diastolic BP, both in normotensive and hypertensive subjects. In addition, in a recent 6-week crossover trial in normotensive overweight and obese subjects, the 3 g/day reduction in salt intake (from 9 g/day to 6 g/day) improved flow-mediated dilation and decreased plasma endothelin-1.

Current diets are estimated to contain 6 g/person/day of salt (≈2400 mg/day of sodium). The American Heart Association recommends a sodium intake of ≈1500 mg/day (≈4 g/day of salt). The World Hypertension League estimated that nearly 30% of hypertension cases might be attributed to a high dietary salt intake; therefore, reduction in the dietary salt consumption should be the first step in the treatment of hypertension. Another wise strategy to decrease BP is to increase the intake of foods rich in BP-lowering compounds. Again, the Mediterranean diet is rich in foods containing BP-lowering agents such as potassium and polyphenols. Potassium is present in fresh fruits, vegetables, and whole grain cereals—all key foods of the Mediterranean diet. A recent population-based study in 1286 subjects has observed an inverse association of urinary potassium excretion, a surrogate marker of potassium intake, with systolic and diastolic BP only in subjects consuming more than 6 g of salt daily, partially counteracting the effects of a high salt diet. Polyphenols are also abundant in fresh fruits, vegetables, whole grains, extra-virgin olive oil, and wine. In a study performed in nonhypertensive high-cardiovascular risk males, red wine polyphenols decreased both systolic and diastolic BP about 6%.

### Mediterranean diet

<table>
<thead>
<tr>
<th>Recommended</th>
<th>Goal</th>
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<tbody>
<tr>
<td>1. Olive oil*</td>
<td>≥4 tbsp/day</td>
</tr>
<tr>
<td>2. Tree nuts and peanuts†</td>
<td>≥3 servings/week</td>
</tr>
<tr>
<td>3. Fresh fruits</td>
<td>≥3 servings/day</td>
</tr>
<tr>
<td>4. Vegetables</td>
<td>≥2 servings/day</td>
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<tr>
<td>5. Fish (especially fatty fish),</td>
<td>≥3 servings/week</td>
</tr>
<tr>
<td>seafood</td>
<td></td>
</tr>
<tr>
<td>6. Legumes</td>
<td>≥3 servings/week</td>
</tr>
<tr>
<td>7. “Sofrito”†</td>
<td>≥2 servings/week</td>
</tr>
<tr>
<td>8. White meat instead of red meat</td>
<td>preferable</td>
</tr>
<tr>
<td>9. Wine with meals (optionally, only</td>
<td>≥7 glasses/week</td>
</tr>
<tr>
<td>for habitual drinkers)</td>
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<table>
<thead>
<tr>
<th>Discouraged</th>
<th>Goal</th>
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</thead>
<tbody>
<tr>
<td>1. Soda drinks</td>
<td>&lt;1 drink/day</td>
</tr>
<tr>
<td>2. Commercial bakery,</td>
<td>&lt;3 servings/week</td>
</tr>
<tr>
<td>sweets, pastries§</td>
<td></td>
</tr>
<tr>
<td>3. Spread fats</td>
<td>&lt;1 serving/day</td>
</tr>
<tr>
<td>4. Red and processed meats</td>
<td>&lt;1 serving/day</td>
</tr>
</tbody>
</table>

*Including oil used for frying or salads, or consumed from meals eaten out of home. In the group allocated to the Mediterranean diet with extra-virgin olive oil, the goal was to consume ≥50 g/day (4 tbsp = 40 g/day) of the polyphenol-rich olive oil supplied, instead of the ordinary refined variety, which is poor in polyphenols.

†In participants allocated to the Mediterranean diet with nuts the recommended consumption was one daily serving (30 g, distributed as 15 g walnuts, 7.5 g almonds, and 7.5 g hazelnuts).

‡Sofrito is a sauce made with tomato, onion, and/or garlic, which is slowly simmered with olive oil.

§Commercial bakery, sweets, or pastries (not homemade), including cakes, cookies, biscuits, or custard.

Table I Summary of dietary recommendations to participants in the Mediterranean groups included in the PREDIMED trial. After reference 5. Estruch et al. N Engl J Med. 2013;368:1279-1290. Copyright © 2013 Massachusetts Medical Society. All rights reserved.
and 2 mm Hg respectively, possibly through a nitric oxide-mediated mechanism. In the PREDIMED trial, polyphenol intake was also negatively associated with BP and prevalence of hypertension. Additionally, subjects allocated to the Mediterranean diet groups of the PREDIMED trial had lower systolic and diastolic BP compared with those allocated to the low-fat diet group at 3 months of intervention, and these effects were maintained for 4 years of follow-up. Since these effects of the Mediterranean diet on BP and other risk factors were observed very early in the trial, it seems that it is never too late to change our dietary habits with an ensuing measurable benefit on the surrogate markers of cardiovascular risk.

Diet, diabetes, and other cardiovascular risk factors
Several epidemiological studies observed an association between higher adherence to the traditional Mediterranean diet and a decreased risk of diabetes. These results have been confirmed in randomized clinical trials that found that intensive lifestyle modifications, which promote weight loss through energy-restricted diets and increased exercise, reduce the incidence of diabetes. In the pilot study of the PREDIMED trial, we already observed that a Mediterranean diet supplemented with extra-virgin olive oil or nuts increases insulin sensitivity at 3 months of the intervention. The final analysis of the effects of the Mediterranean diet on incident diabetes in the PREDIMED cohort demonstrated that a Mediterranean diet supplemented with extra-virgin olive oil decreased new cases of diabetes by 40% compared with a low-fat diet, after a follow-up of nearly 4 years. These results are an extension of prior studies showing that long-term lifestyle intervention reduces the incidence of diabetes in high-risk subjects, but added that the diet may exert this beneficial effect by itself, without other lifestyle changes.

Replacing carbohydrates with dietary fat lowers the plasma triglyceride concentration and increases the high-density lipoprotein cholesterol (HDL-C) concentration, while substituting monounsaturated fatty acids for saturated fatty acids lowers low-density lipoprotein cholesterol (LDL-C) concentration. In the PREDIMED trial, the lipid profile did not change in the low-fat diet group (control group), while HDL-C increased in both the Mediterranean diet groups, especially when supplemented with extra-virgin olive oil. This effect has been attributed to the minor components of extra-virgin olive oil; mainly polyphenols. Since low-fat diets usually lower both plasma HDL-C and LDL-C concentrations, a fat-rich Mediterranean diet may be a better nutritional option for high-risk subjects. In addition, the Mediterranean diet shifts lipoprotein subfractions to a less atherogenic pattern. Thus, the Mediterranean diet, especially when it is supplemented with nuts, reduces plasma concentrations of medium-small and very small LDL-C particles, decreases LDL-C particle number, and increases large LDL-C particle concentration, whereas both the Mediterranean diets used in the PREDIMED trial, increased large HDL-C concentration. These changes, which were evident within 1-year of intervention with the Mediterranean diet, may contribute to the reduction in cardiovascular events observed in the PREDIMED trial.

Conclusions
There is ample evidence supporting the notion that diet has a direct effect on several cardiovascular outcomes. A Western diet rich in saturated fats, sugar, and salt, and poor in fiber, minerals, vitamins, and antioxidants increases cardiovascular risk perhaps by promoting inflammation and, subsequently, the appearance and progression of atherosclerosis and hypertension. In contrast, the traditional Mediterranean diet decreases the incidence of cardiovascular events and mortality by reducing classical and novel vascular risk factors. These protective effects may be even greater if we upgrade the health effects of this dietary pattern by reducing dietary salt intake. Thus, we encourage clinicians to promote the Mediterranean diet and reduction in salt intake to reduce the cardiovascular risk for their patients.

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Epicardial adipose tissue: a simple marker of obesity or a complex mediator of cardiovascular disease?

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Abstract  
Epicardial adipose tissue represents the layer of adipose tissue confined between the myocardium and visceral pericardium. Although for long its significance has remained unclear, there is now emerging evidence that suggests it is a potent marker of cardiovascular risk and is related to clinical outcomes. The current article reviews the anatomy and function of epicardial adipose tissue, the methods of its evaluation, its relationship to cardiovascular disease, and potential treatment strategies. Heart Metab. 2014;63:13–17

Keywords: Atherosclerosis; cardiovascular disease; epicardial adipose tissue; pathophysiology.

There has been an increase in obesity and diabetes mellitus in recent years and this has impacted the prevalence of additional metabolic and cardiovascular disorders. Whereas subcutaneous adipose tissue (SAT) and visceral abdominal adipose tissue (VAT) have received much attention as potential culprits, epicardial adipose tissue (EAT) has largely been neglected. In the following review, we explore the increasing pathophysiological understanding of this intriguing fat depot over the last decade, and its potential contribution to cardiovascular disease.

Epicardial adipose tissue  
There are two major types of adipose tissue, each with different physiological roles. White adipose tissue is predominantly located within the subcutaneous layers (SAT) and around the major organs (VAT). Here, its primary function is to serve as a storage organ for triglycerides and free fatty acids during fasting, starvation, or exercise. Brown adipose tissue, on the other hand, is located in clusters around the clavicles, scapulae, and heart. It is a more metabolically active fat depot and contains numerous mitochondria that confer to it a thermogenic capability.

Epicardial adipose tissue is brown adipose tissue and is located between the myocardium and the visceral pericardium. It constitutes 20% of the heart’s mass while covering 80% of its surface. In the nonobese state, EAT is likely to have a number of beneficial effects. As a reservoir of free fatty acids, it has the potential to provide an energy source for the myocardium when metabolic requirements are high and to serve as a buffer for high circulating fatty acid levels. Epicardial fat is also known to secrete adiponectin and adrenomedullin, which
are known to have important anti-inflammatory and anti-atherogenic effects. Finally, the EAT layer may provide cushioning for the coronary arteries and reduce torsional forces.

**Imaging modalities**

EAT can be measured by echocardiography, computed tomography, and cardiac magnetic resonance imaging (CMRI). On 2-dimensional transthoracic echocardiography, epicardial fat can be best visualized in the parasternal long-axis and short-axis views as an echo free space between the myocardium and visceral layer of the pericardium. In the parasternal long-axis plane, using the aortic annulus as a landmark, its thickness is usually measured perpendicularly to the right ventricular free wall of the right ventricle at end systole in three cardiac cycles.\(^5\)

End-systolic measurements are preferable to diastolic measurements owing to compression of EAT during systole. If the amount of EAT is large (>15 mm), then the appearance may be echogenic in nature, which may aid in distinguishing it from a significant pericardial effusion.

One of the difficulties with the incorporation of echocardiographic EAT measurements into clinical practice is the lack of appropriate normal ranges. There is a wide variation in EAT measurements from a minimum of 1 mm to a maximum of 23 mm that reflects the wide variation in abdominal adipose tissue deposits among patients undergoing routine echocardiography.\(^6\) Of the few studies that have been performed, it has been shown that a 6 to 7 mm rim of EAT tissue most likely represents a normal range for men and women undergoing routine echocardiograms. For the prediction of a metabolic syndrome, a threshold of 9.5 mm for men and 7.5 mm for women has been proposed.\(^6\)

In general, cardiac computed tomography has superseded echocardiography as the technique of choice for the accurate quantification of EAT owing to its high spatial resolution and reproducibility. The volume of EAT can be calculated by identifying the superior and inferior boundaries of the pericardium and then tracing around the parietal pericardium using 5 to 10 control points in sequential axial views. From these points, a dedicated software is able to generate a smooth and closed pericardial contour. Epicardial fat volume is then calculated by summing the contiguous 3-dimensional voxels that occur within the Hounsfield Units (HU) range for adipose tissue (-190 and -30 HU; Figure 1).\(^7\)

CMRI also has the capability to measure epicardial adipose tissue thickness anterior to the epicardial surface on the right ventricular free wall on the horizontal long-axis, 4-chamber, and short-axis views.\(^8\) Tracing around the epicardial fat on serial short-axis slices can also quantify the absolute amount of epicardial fat.\(^9\)

**Potential mechanisms of cardiovascular disease**

In obesity, diabetes, metabolic syndrome, and hypertension, the protective effects of EAT are overcome by its ability to promote vascular dysfunction and atherogenesis.\(^10\) An expansion of EAT occurs, which is accompanied by tissue hypoxia and an infiltration of macrophages and T cells. This reduces the production of protective adipokines such as adrenomedullin and adiponectin,\(^11\) and increases the production of detrimental cytokines such as leptin, resistin, chemerin, interleukin-6, and tumor necrosis factor \(\alpha\) (TNF-\(\alpha\)).\(^12\)

Adiponectin expression from EAT has been shown to be lower in patients with coronary artery disease (CAD) compared with patients without CAD,\(^11,13\) whereas proinflammatory cytokines are higher in samples of EAT taken from patients with CAD, relative to SAT.\(^14\) These findings have led investigators to propose that EAT may exert its biological effect by a local paracrine or vasocline effect on the adjacent myocardium and coronary vasculature.\(^15\)

**Atherosclerosis**

Primary evidence supporting a pathogenic role of EAT in cardiovascular disease is its association with coronary atherosclerosis.\(^1,16\) In the Framingham Heart Study,\(^16\) Rosito et al demonstrated, in 1155 patients, an independent relationship of epicardial fat volume to coronary calcium after adjustment for conventional cardiovascular risk factors, body mass index (BMI), and waist circumference. Similarly, in the Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research (EISNER) Registry,
Dey et al showed in 201 healthy asymptomatic individuals that EAT was independently associated with coronary calcium. A number of additional studies have also shown a relationship of EAT with the extent and severity of CAD angiographically, and plaque morphology, progression, and vulnerable plaque features.

**Myocardial and arrhythmic heart disease**
In addition to its association with atherosclerotic coronary disease, EAT has also been implicated in other cardiovascular disease states. In a study of 273 patients, Al Chekakie et al demonstrated increased epicardial fat volume in 197 patients with persistent or paroxysmal atrial fibrillation when compared with 76 patients in sinus rhythm. This relationship was independent of diabetes mellitus, hypertension, left atrial size, and BMI and suggests that EAT may have a direct pathogenetic effect on left atrial myocardium. Other studies have also shown associations of EAT with diastolic function abnormalities and also left ventricular structural and functional changes.

**Prognostic value**
A number of studies have demonstrated that EAT may be an important prognostic marker of cardiovascular events. Cheng et al compared epicardial fat volume (EFV) between 58 patients who developed major adverse cardiac events with 174 propensity-matched controls. The authors observed higher EFV for those patients who developed major adverse coronary events (MACE) when compared with event-free controls with similar cardiovascular risk profiles. In another study of 760 patients with acute chest pain, all of whom underwent coronary computed tomography, Forouzandeh et al investigated whether EAT improved risk stratification beyond calcium scoring. The authors showed that both coronary artery calcium stores (CACS) and EAT were independently associated with MACE in patients with chest pain.

![Epicardial fat volume measurement using the QFAT software (Cedars-Sinai Medical Center, Los Angeles, California).](image)

1a. Shows a noncontrast enhanced cardiac computed tomographic scan of the chest. 1b. The pericardium is marked on axial slices from the branching of the main pulmonary to the inferior aspect of the heart where the posterior descending artery is first seen within the inferior atrioventricular groove. 1c. The QFAT software then automatically calculates the volume of epicardial adipose tissue within the visceral pericardium as those voxels with a Hounsfield Unit (HU) value ranging from 190 to 30 HU (red). Transthoracic fat is calculated as adipose tissue outside of the pericardium and is marked as yellow.
and that EAT may have added value in patients with a CACS >400 Agatston units. Finally, Mahabadi et al studied 4093 participants from the Heinz Nixdorf Recall Study and investigated whether quartiles of EFV were related to incident coronary events.27 The authors showed that coronary events increased with each quartile increase of EAT and that a doubling of EAT was associated with a 1.5-fold increase for coronary events, even after adjusting for conventional cardiovascular risk factors and CACS.

Modifying epicardial fat: lifestyle, weight reduction, and pharmacotherapy
Given the association of EAT with cardiovascular disease and clinical outcomes, there have been a number of studies that have attempted to reduce its quantity. In an observational study of 374 healthy asymptomatic individuals, Nakazato et al showed that ≥5% weight change resulted in EFV changes.28 Iacobellis et al introduced a severe calorie restriction program (900 kcal/day) to 20 subjects with severe obesity.29 At six months there was a 20% reduction in body weight, 19% reduction in BMI, 23% reduction in waist circumference, and 32% reduction in epicardial fat measured echocardiographically. Kim et al studied the effects of exercise training without calorie restriction on 24 obese middle-aged men.30 Following a 12-week supervised exercise training program there was a significant decrease in epicardial fat thickness measured over the right ventricular free wall on echocardiography. This change was greater than that of the initial waist circumference, BMI, and weight, and was independently related to changes in visceral adipose tissue and systolic blood pressure. Similar findings have also been demonstrated in patients undergoing bariatric surgery for severe obesity. Iacobellis et al showed a mean reduction of 23% in echocardiographically measured fat thickness at 8 months in 23 patients who underwent bariatric surgery.6 Gaborit et al showed using ‘H magnetic resonance spectroscopy31 that bariatric surgery resulted in substantial weight loss in a study of 23 patients and that this was accompanied by a reduction in insulin resistance parameters, an improvement in cardiac function parameters, and a significant reduction in epicardial fat volume. Finally, Schinkel et al showed significant changes in epicardial fat upon MRI in 10 morbidly obese patients with type 2 diabetes within 16 weeks following gastric bypass surgery.32

There have been limited studies investigating the use of medication on epicardial adipose tissue. In a substudy of the BELLES trial (Beyond Endorsed Lipid Lowering with Electron Beam Tomography Scanning), Alexopoulos et al studied the effects of 80 mg/day of atorvastatin versus pravastatin 40 mg/day for one year in postmenopausal women.33 The authors showed greater EAT regression (-3.4%) with atorvastatin than in the pravastatin treated arm (-0.83%), which suggests that higher intensity statins may confer a beneficial effect on epicardial fat (potentially by their anti-inflammatory effect).

Conclusions
Over the last decade our understanding of the physiological function and pathological effects of EAT have increased substantially. Studies indicate that EAT is likely to represent a useful cardiovascular risk marker and one that has the ability to potentiate a variety of different cardiovascular disease states and affect the clinical outcome. The modulation of EAT volume using various lifestyle interventions and pharmacotherapy to manage potential cardiovascular complications shows promise, however, further outcome data is required prior to their widespread recommendation.

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Gut microbes and cardiometabolic risk

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Abstract

Obesity, type 2 diabetes mellitus, and consequent cardiovascular disease are major public health issues worldwide. There is growing evidence that the increasing prevalence of obesity cannot only be explained by a combination of genes, nutritional habits, and decreased physical activity. An additional factor influencing human metabolism and adiposity, which has recently been considered, is the intestinal microbiota. Obesity is associated with substantial changes in the composition and metabolic function of the commensal bacterial strains living within the human gut. However, the molecular mechanism(s) that mediate the effects of the gut microbiota on host metabolism and metabolic disease are still largely unknown. This review summarizes the latest results in this fascinating new area of research. Heart Metab. 2014;63:18–22

Keywords: Cardiovascular disease; gut microbiota; insulin resistance; obesity.

We are in the midst of a worldwide obesity epidemic, a major factor in the development of common medical conditions such as type 2 diabetes, dyslipidemia, and cardiovascular disease. Obesity is a multifactorial disorder influenced by a mixture of genetic and environmental factors. During the last few years, a growing body of literature points toward a role for the gut microbiota and its function that is encoded by its genome (also called the microbiome) in various diseases ranging from gastrointestinal tract diseases, such as inflammatory bowel disease, to obesity.1,2 This review discusses the most recent findings and insights into the relationship between the human microbiota, obesity, and insulin resistance.

The human gut microbiota

The adult human intestinal tract contains a large variety of microorganisms, of which bacteria are the most dominant and diverse. The size of this population, up to 100 trillion/g of intestinal material, far exceeds that of all other microbial communities associated with the body's surface. As a whole, the microbiome is more than 100 times larger than the human genome.3,4 Accordingly, our microbiota can be viewed as a forgotten organ that contributes to overall metabolism and plays a role in converting food into nutrients and energy.5

Until recently, our understanding of human gut microbiota was limited, as the majority of the dominant (anaerobic) gut microbiota cannot yet be cultured. The development of 16S ribosomal RNA (rRNA) and genome sequence–based methods has improved the understanding of the gut microbial ecology in humans and mice.6 The diversity of the gut microbiota in both mice and humans is low at the phylum level, where the majority of species (>90%) belong...
to Bacteroidetes, Firmicutes, and Actinobacteria. In contrast, the microbial diversity at the species level is very high, which was confirmed in a recent metagenomic sequence analysis that revealed a reference set of over 3 million genes in over 100 subjects.

The intestinal microbiota of the newborn human was thought to be essentially sterile, but recent data suggest that modest bacterial translocation via placental circulation occurs antenatally and is likely to provide a primitive bacterial community to the meconium. Although the new concept of fetal intestinal colonization remains controversial, ongoing studies using 16S ribosomal RNA (rRNA) gene pyrosequencing to characterize the bacterial population in the meconium of preterm infants suggest that the bacteria of the maternal intestine are able to cross the placental barrier and act as the initial inoculum for the fetal gut microbiota. After transformation to the adult-type, the gut microbiota remains remarkably constant, fluctuating around an individual core of stable colonizers. The composition of the microbiota is considered to be influenced by the host genotype, colonization history, the physiology of the host and environmental factors.

Several studies showed that the genetic makeup of the individual influences the composition of the core microbiota as was confirmed in a recent analysis of obese and lean twins. The human gut microbiota is shared among family members, but each person’s gut microbial community varies in the specific bacterial lineages present, with a comparable degree of covariation between twin pairs. However, there was a wide array of shared microbial genes among sampled individuals, comprising an extensive, identifiable ‘core microbiome’ at the gene, rather than at the organism lineage level, suggesting that certain functions are tolerated, or even transmissible, traits in host metabolism.

**Gut microbiota and obesity**

The initial link between gut microbial ecology and obesity was made by Gordon et al. They found that young conventionally reared mice have 42% more total body fat and 47% more gonadal fat than germ-free mice. This was surprising since the control mice had a lower caloric intake than germ-free mice. The presence of microbiota per se apparently increased the energy yield from the host organism’s diet. Following-up on this observation, the same group demonstrated that colonization of young germ-free mice with microbiota from conventionally reared mice produces a 60% increase in body fat mass associated with increased insulin resistance, despite lower energy intake. Moreover, they also demonstrated that fecal transplantation with microbiota from obese mice (ob/ob) results in a significantly greater increase in total body fat than colonization with microbiota from lean donors. Again, these findings underscore the increased ability of microbiota, in obese animals, to extract energy from the diet and provide it to the host.

The gut microbiota does not influence only host adiposity through energy extraction from the diet, but also by messenger molecules that influence metabolism throughout the body. For instance, the gut microbiota regulates an important gut-derived regulator of lipid metabolism; fasting-induced adipose factor (FIAF) also referred to as angiotensin-like protein 4 (ANGPTL4). FIAF regulates fatty oxidation in both muscle and adipose tissue. Microbial colonization of the gut suppresses FIAF expression, leading to suppression of lipoprotein lipase (LPL), and hence, to a greater proportion of triglycerides in adipose tissue. Furthermore, germ-free Fiaf-knockout mice are no longer protected against diet-induced obesity. Bäckhed et al also demonstrated that germ-free mice have increased levels of phosphorylated AMP-activated protein kinase in the muscle and liver, which would stimulate free fatty acid oxidation. Therefore, germ-free animals seem to be protected from diet-induced obesity by two complementary, but independent mechanisms, which results in decreased fatty acid storage, elevated levels of FIAF, and increased AMP-activated protein kinase activity.

Several studies in both mice and humans demonstrated that obesity is associated with an altered gut microbial ecology, hallmarked by lower microbial diversity and decreased levels of Bacteroidetes. The shift in microbial composition is associated with alterations in the gut microbial metagenome, notably there is an enrichment of genes involved in energy
harvesting. Ley et al analyzed 5088 bacterial 16S rRNA gene sequences from fat mice (ob/ob phenotype), lean mice (ob/+ phenotype), and wild-type mice and showed that obese animals have a 50% reduction in the abundance of Bacteroidetes and a proportional increase in Firmicutes. A subsequent metagenomic analysis of these same microbial communities, which was based on shotgun sequencing of the microbial community DNA, showed enrichment in genes involved in energy extraction from food in the microbiome from ob/ob mice relative to the microbiome from ob/+ mice. A microbiota with a greater energy extraction efficiency resulted in less leftover energy in feces and higher levels of short-chain fatty acids (SFCAs) in the cecum.

Similar to these animal experiments, Bacteroidetes tend to decrease and Firmicutes increase in the feces of obese compared with lean humans. Obese people harbor fewer Bacteroidetes and more Firmicutes than lean controls, and after following a carbohydrate- or fat-restricted low-energy diet, Bacteroidetes increased and Firmicutes decreased. These data suggest a relationship between obesity and diversity of intestinal microbiota. However, other studies were not able to support these specific findings, which is most likely due to differences in formulation between (local) diets, as dietary composition has recently gained interest as one of the most important drivers of gut microbiota composition.

**Gut microbiota, low grade inflammation, and type 2 diabetes**

Several studies provided evidence that gut microbial composition is associated with insulin resistance. As expected, the decreased adiposity in germ-free mice is associated with improved insulin sensitivity and glucose tolerance. However, gut microbiota may also have direct effects on host glucose metabolism.

One way for bacteria to affect insulin sensitivity is through metabolic inflammation caused by elevated endotoxin levels. Lipopolysaccharide (LPS) is continuously produced in the gut through lysis of gram-negative bacteria. LPS is a powerful trigger for secretion of a series of proinflammatory cytokines. Continuous subcutaneous low-rate infusion of LPS led to excessive weight gain and insulin resistance in mice, without

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**Fig. 1** The major pathways by which intestinal microbiota can alter human cardiometabolism. Chronic bacterial translocation (due to increased intestinal permeability) can drive systemic inflammation leading to macrophage influx into (visceral) adipose tissue, activation of hepatic Kupffer cells resulting in NAFLD and insulin resistance. Moreover, SCFAs normalize intestinal permeability and alter de novo lipogenesis and gluconeogenesis via reduction of FFA production by visceral adipose tissue. Finally, TMAO can accelerate atherosclerosis and vascular inflammation via influx of macrophages and cholesterol accumulation by up-regulation of macrophage scavenger receptors and reduction in reverse cholesterol transport.

**Abbreviations:** FFA, free fatty acids; NAFLD, non-alcoholic fatty liver disease; SCFAs, short chain fatty acids; TMAO, trimethylamine-N-oxide.
altering energy intake. Le Chatelier et al showed that an altered diet affects gut microbiota composition, which was associated with an adverse cardiovascular risk profile including glucose intolerance, dyslipidemia, and a chronic low grade (LPS-driven) inflammatory state (Figure 1). Recent association studies by Qin et al (performed in China) and Karlsson et al (performed in Europe) reported differences in microbiota composition and diversity between a cohort of patients with type 2 diabetes and a group of healthy individuals. Independently, each study found that the microbiota of subjects with type 2 diabetes had a lower proportion of butyrate-producing Clostridia (Roseburia species and Faecalibacterium prausnitzii), and a greater proportion of nonbutyrate producing Clostridia as well as pathogens such as Clostridium c Frostidioforme. Moreover, Karlsson et al found that an increased proportion of Lactobacillus gasseri and Streptococcus mutans (commensal bacteria in the mouth and upper intestinal tract) were predictive of developing type 2 diabetes in this cohort of obese but otherwise healthy postmenopausal females. Qin et al observed a greater proportion of Escherichia coli, which produces LPS to cause endotoxemia, in patients with type 2 diabetes. These studies raise interest in the association between intestinal bacterial composition, reduced butyrate production, and chronic low-grade inflammation leading to type 2 diabetes.

Gut microbiota and cardiovascular disease

Besides obesity, intestinal microbiota might also be involved in atherogenesis. Specific dietary nutrients characterized by trimethylamine groups (e.g., choline, phosphatidylcholine, and carnitine) are metabolized into the atherogenic compound trimethylamine-N-oxide (TMAO) by bacteria (Figure 1) and were found to be independent risk factors for cardiovascular events. Studies using germ-free mice or mice given broad-spectrum antibiotics demonstrated that the intestinal microbiota is required for the formation of TMAO. Bacterial colonization of germ-free mice increases their plasma levels of TMAO, indicating that the intestinal microbiota are required for generation of this compound from sources of dietary choline or carnitine (such as eggs, milk, and red meat). For example, carnitine is an abundant nutrient in red meat, and the intestinal microbiota mediates production of TMAO from dietary L-carnitine.

Modulation of gut microbiota composition

Emerging data suggest that an imbalance in the composition of gut microbiota is related to obesity and metabolic disease. Taking a reductionist approach, directly interfering with gut microbiota may ameliorate obesity and the associated insulin resistance. Bile acids have been highlighted as crucial metabolic integrators and signaling molecules involved in the regulation of metabolic pathways including glucose, lipid, and energy metabolism. Interestingly, short term administration of antibiotics in humans significantly altered the fecal bile acid with a reduction in secondary bile acids compared with primary bile acids as well as deterioration of insulin sensitivity. Another intervention to support the causal role of intestinal microbiota in human metabolism and insulin resistance could be the use of fecal transplantation. We examined this hypothesis by transplantation of feces from a lean human donor in participants with a metabolic syndrome (body mass index ≥30 kg/m²; fasting plasma glucose >5.6 mmol/L, with no medication use). In this double-blind randomized controlled trial we investigated the effect of transplantation of donor feces on glucose homeostasis and lipid metabolism. Following poly-ethylene-glycol bowel lavage through the duodenal tube, subjects were randomized to either allogenic (from a lean male donor with body mass index <23 kg/m², n=9), or autologous (reinfusion of own collected feces, n=9) fecal transplantation. We studied changes in the gut microbiota composition, glucose metabolism (hepatic and peripheral insulin sensitivity as assessed by hyperinsulinemic euglycemic clamp with stable isotopes), and fasting lipid profiles. We found that bacteria producing short chain fatty acids (SCFA) were significantly upregulated in both small intestinal biopsies and fecal samples of metabolic syndrome patients that were treated with allogenic donor feces. However, the exact nature of this symbiotic relationship remains to be elucidated. With high-throughput approaches aimed at documenting diversity at the metagenome level, we might actually be able to unravel the role of the gut microbiota in human metabolism and use this technique as a working tool to discover novel diagnostic and therapeutic capacities of the intestinal microbiota.

Conclusion

Accumulating data from both patients and animal models relate imbalances in the composition of the
gut microbiota to obesity and its associated diseases. However, the exact role of the microbiota and the mechanism mediating its impact on metabolic functions are just beginning to be unraveled. The approaches used to characterize gut microbiota vary widely, which might explain, in part, why the specific alterations in the microbiota can also vary between studies. Comparisons between studies will require a uniform method for measuring the microbial composition. However, irrespective of the specific changes observed in microbial communities, evidence suggests that gut microbiota do indeed respond and contribute to the host’s energy balance. They may do this by variable and possibly interactive signaling mechanisms. The major challenge will be to identify and modulate the gut microbiota (or its signaling to the host) to prevent disease and promote health.

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Focus on trimetazidine: effects on diet and the heart

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Abstract
Trimetazidine, a clinically effective antianginal agent that has no negative inotropic, chronotropic, or vasodilator properties, mediates a general improvement in cardiac metabolism. It has been suggested that trimetazidine may exert its antianginal effect by inhibiting fatty acid oxidation and improving glycolysis and glucose oxidation. Trimetazidine is a partial inhibitor of long-chain 3 ketoacyl-coenzyme A thiolase, the enzyme catalyzing the last step of free fatty acid β-oxidation; therefore, inhibiting fatty acid oxidation. The inhibition of free fatty acids oxidation with trimetazidine in coronary artery disease patients with or without diabetes improved cardiac metabolism at rest and during stress. For this reason, the recent European Society of Cardiology guidelines on stable coronary artery diseases suggest that trimetazidine be used as an add-on drug that improves cardiac metabolism. Heart Metab. 2014;63:23–28

Keywords: Adenosine triphosphate; angina; ATP; ATP/O₂; β-oxidation; cardiac metabolism; fatty acid oxidation; ischemia; trimetazidine.

Trimetazidine is a clinically effective antianginal agent that has no negative inotropic, chronotropic, or vasodilator properties. Thus, trimetazidine is different from the “classical” antianginal agents such as nitrates, β-blockers, calcium channel blockers, or ivabradine as it does not affect myocardial oxygen consumption and blood supply. Experimentally, the beneficial effect of this agent has been attributed to the preservation of myocardial energy stores,¹ reduction in intracellular acidosis,² calcium overload,³ and free radical injury caused by ischemia.⁴ It follows that the effects of trimetazidine are mediated by a general improvement in “cardiac metabolism,” which is threatened and/or altered in: (i) the condition of transient oxygen deficiency such as angina; (ii) prolonged ischemia such as myocardial infarction (MI); or (iii) chronic hypoxia such as heart failure (HF). A relevant question is what the overused wording “cardiac metabolism” means and how it is altered in pathological conditions and, more relevantly, how it can be changed for the better by trimetazidine, which is the main topic of this issue of Heart and Metabolism.

The purpose of this short review is to analyze the meaning of “cardiac metabolism” for the clinician and to address the existing evidence that trimetazidine exerts an antiangiial effect. By no means is the purpose to review the complexities of heart metabolism, which has been properly addressed elsewhere.⁵,⁶,⁷ The idea is to try to provide the reader with the essential information to help decide when, why, and in which patients to add trimetazidine to the classical
antianginal agents. As the prevalence of type 2 diabetes mellitus is rapidly increasing and as the distinct metabolic profile of diabetes appears to be important for increasing the risk for coronary artery disease (CAD), a subchapter is dedicated to this topic.

The daily work of the human heart is simply extraordinary: approximately 100 000 beats and more than 9000 liters of blood is ejected into the circulation, which travels about 136 000 km (this is how long our ultramicroscopic circulation is!) in 27 seconds. Obviously, to sustain such continuous work (for all of our life, night and day), the heart consumes a great amount of energy in the form of adenosine triphosphate (ATP), which is produced by the mitochondria (provided there is enough oxygen to support mitochondrial oxidation) and is transferred to the cytosol. Although it is difficult to be precise, it is estimated that the daily energy production of cardiac mitochondria ranges between 10 to 30 kg of ATP. It may sound impossible, but it is not. It is a continuous cycle: ATP is produced by the mitochondria and it is immediately utilized mainly in the cytosol to allow the synchronous contraction of the myofilaments (systole) and the extrusion of Ca²⁺ from the myofilaments to the sarcoplasmic reticulum, the extracellular space, or into the mitochondria (diastole). Of course, ATP is also necessary to support several other processes that are linked to the maintenance of the myocyte structure and function. There is no doubt that the heart is the highest energy-consuming organ in the body; consequently, it contains the highest number of mitochondria compared with other organs. This also explains why the heart is so dependent on oxygen delivery through the coronary arteries to feed mitochondrial oxidation. Interestingly, the myocardial oxygen reserve is almost nonexistent and is just enough to support a few heartbeats. Similarly, the myocardial ATP pool is very limited; the main myocardial energy reserve is represented by creatine phosphate (CP).

Free fatty acid and carbohydrate metabolism
The wording “cardiac energy metabolism” refers to the complex biochemical process that allows the heart to produce enough ATP to support its function and the physiological maintenance of the myocyte structure. As it is shown in Figure 1, the ultimate major source of mitochondrial energy production lies in extracellular carbohydrates and free fatty acids (FFAs). Interestingly, the heart has the unique ability to use either carbohydrates (mainly glucose and lactate) or FFAs with continuous alternation between the two, according to their arterial concentrations (ie, after a meal, as the arterial concentration of carbohydrates increase, glucose is the preferred substrate). The metabolism of these substrates merges because, ultimately, they both produce acetyl-CoA, a 2-carbon molecule that is oxidized via the Krebs cycle. In this way, their intrinsic chemical energy can be released for ATP production by oxidative phosphorylation.⁵⁻⁷ Carbohydrate and FFA degradation to acetyl-CoA, however, involves different metabolic routes, β-oxidation for FFA and glycolysis for carbohydrates (Figure 1).

The metabolism of FFAs is complex. FFAs are generally bound to plasma proteins, namely albumin. They cross the heart membrane (sarcolemma) by passive diffusion, probably with the involvement of a specific intracellular binding protein in the cytosol and are activated at the expense of ATP and coenzyme A (CoA) to form long-chain acetyl-CoA. These cannot enter the mitochondrial matrix where the enzymes for their β-oxidation are located. For this purpose, carnitine is required. Due to the activity of the carnitine transport system, long-chain acetyl-CoA reaches the inner mitochondrial space and can enter the β-oxidation cycle, where their long molecule (16 to 18 carbon) is demolished into several acetyl-CoA molecules that only have 2 carbon
fragments. The cleavage occurs at the level of the second carbon atom, which is the β-position. During the fragmentation of the FFAs, the intrinsic energy contained in the long molecule is released with the formation of FADH₂ and NADH₂, which in turn, are able to provide the protons required for the eventual production of ATP. In the presence of oxygen, the actual ATP production from FFAs depends on which FFA is involved. If we take palmitic acid as an example, 35 ATP are produced during β-oxidation. In addition, each molecule of palmitic acid (16 carbon) produces 8 acetyl-CoA, which, when passing through the Krebs cycle, generates a total of 131 ATP. ATP is used for activation of acetyl-palmitoyl-CoA. Thus, the total ATP production per one molecule of palmitic acid is 130 ATP molecules, with an ATP/O₂ ratio of 130/23 (meaning that 23 oxygen molecules are used during the entire process), providing an ATP/O₂ ratio of 5.6.⁷

Carbohydrates are broken down by glycolysis, the process that converts one molecule of glucose (actually glucose-6-phosphate, a molecule with 6 carbons) to 2 molecules of pyruvate (a molecule with 3 carbons). For each glucose converted to pyruvate, 4 molecules of ATP are made, but 2 are used to form glucose-6 phosphate, so the net ATP synthesis is 2 ATP. Glycogen, which represents the carbohydrates stored in the myocardium, can form glucose-6-phosphate without requiring ATP. Therefore, for each 6-carbon units of glycogen broken down to pyruvate, 4 ATP will be generated. Such a small production of ATP occurs in the cytosol, not in the mitochondria and, therefore, does not require oxygen. This is particularly relevant under the condition of ischemia (i.e., during an angina attack) as it is the only way to allow the formation of ATP in the absence of an oxygen supply. As a result of such a peculiarity of ATP production in the absence of oxygen, glycolysis represents the so-called “anaerobic” metabolism and is the reason why glucose is a better substrate than FFAs for the ischemic heart.

Pyruvate is subsequently converted, this time by an aerobic (oxygen requiring) metabolism to acetyl-CoA. This process occurs in the mitochondrial matrix and requires the activity of a complex enzyme named pyruvate dehydrogenase that allows pyruvate to enter the mitochondria and catalyze the reactions, converting pyruvate into acetyl-CoA.⁶,⁷ During this process and with the entry of acetyl-CoA into the Krebs cycle, a further 36 ATP molecules are made, providing an ATP/O₂ ratio of 6, slightly higher than that of palmitate. However, it should be considered that 2 ATP are also formed in the cytosol without any oxygen consumption, yielding a total of 38 ATP per molecule of glucose with an ATP/O₂ ratio of 38/6, providing an ATP/O₂ of 6.3.

**Clinical effects of metabolism on heart function**

During ischemia, due to the reduction in oxygen availability, there is a severe restriction of mitochondrial function, which leads to accumulation of acetyl-CoA accompanied by potential harmful effects including detergent-provoked damage of membranes and the obvious inhibition of ATP production. At the same time, anaerobic glycolysis is accelerated with an increase in glucose uptake and glycogen degradation because of the breakdown of the remaining ATP and CP (the energy reserve of the myocardium). Pyruvate, however, can no longer enter into the mitochondrial matrix and it is converted into lactate, which is washed out by the myocytes into the extracellular space. Such an accumulation of end products that includes lactate, NADH₂, and protons has harmful effects accelerating the ischemic process. Clinically, the release of protons and lactate causes intracellular and extracellular acidosis and, consequently, the typical angina pain (Figure 2). At the same time, acidosis interferes with all of the intracellular calcium movements through the sarcolemma and the sarcoplasmic reticulum. Clinically, this results in the regional left ventricular (LV) dyskinesia or even akinesia, which is always present and coincides with the angina pain. In addition, the concomitant decline of ATP in the ischemic myocytes causes a reduction in the uptake of calcium into the sarcoplasmic reticulum and a
decreased activity of the sarcolemma calcium pump, with an increased calcium level in diastole and poor diastolic relaxation. Electrophysiologically, increased cytosolic calcium can also result in arrhythmias dependent on the formation of delayed depolarization. The accumulation of FFAs, consequent to the inactivation of mitochondrial function, also promotes further ischemic damage. An increased level of FFAs or of their metabolic byproducts will cause membrane damage, directly or indirectly, by the formation of lysophosphoglycerides. Increased membrane damage is likely to be associated with arrhythmias, particularly in the presence of high circulating catecholamines. Membrane damage further alters calcium metabolism, resulting in massive overload of the ion with severe relaxation impairment.\textsuperscript{5,9,10} Figure 3 shows the drastic deleterious effect of palmitate vs glucose as a substrate for isolated rabbit hearts perfused under ischemic conditions (coronary flow reduction from 24 to 3 mL/min). When FFA (palmitate) is used as an ischemic substrate, diastolic pressure starts to increase after 15 minutes of ischemic perfusion suggesting severe relaxation impairment. On reperfusion, there is a partial recovery of the pre-ischemic developed pressure suggesting that myocytes are still viable. At the end of reperfusion, mitochondrial calcium is not increased and their capacity to produce ATP is retained. On the contrary, substitution of glucose with palmitate causes massive, irreversible damage after 30 minutes of ischemic perfusion.

**Trimetazidine mode of action**

The data reported in Figure 4 are relevant to explain the mechanism of action of trimetazidine as it has been suggested that it may exert its antianginal effect by inhibiting fatty acid oxidation and improving glycolysis and glucose oxidation.\textsuperscript{10-12} Fantini et al\textsuperscript{13} demonstrated that trimetazidine reduces in vitro mitochondrial respiratory activity in a substrate dependent manner: palmitate oxidation is markedly reduced, but not that of pyruvate, glutamate, or citrate. Later, Kantor et al\textsuperscript{13} showed that in isolated rabbit hearts under aerobic conditions, trimetazidine does not influence substrate metabolism, while under ischemic conditions it causes a switch in the source of acetyl-CoA for the Krebs cycle from fatty acid β-oxidation to glucose oxidation. This is not due to a direct stimulation of pyruvate dehydrogenase (PDH), but rather an indirect stimulation of PDH secondary to less fatty acid oxidation, which is because β-oxidation is a key determinant of PDH activity.\textsuperscript{14} Trimetazidine is a partial inhibitor of long-chain 3 ketoacetyl-CoA thiolase, the enzyme catalyzing the last step of β-oxidation.\textsuperscript{13} This, in turn, stimulates PDH and oxidation of pyruvate, with activation of anaerobic glycolysis.

**Fig. 3** Effect of palmitate vs glucose on an ischemic heart.

**Fig. 4** Metabolic effect of trimetazidine. Effects of different substrate (glucose A and palmitate B) on the mechanical (upper panels) and isolated mitochondrial function of isolated and perfused rabbit hearts under aerobic ischemia (coronary flow 3 ml/min) and aerobic reperfusion. At the end, mitochondria were harvested and their ATP production and Ca\textsuperscript{2+} content determined. Palmitate caused a massive increase of diastolic pressure (index of impaired relaxation) already after 30 mins of ischemic perfusion and no recovery during reperfusion. Glucose exerted a protective effect. Adapted from O. Visioli, F. Di Lisa, R. Raddino, R. Ferrari. Estaratto dal volume: GIUSEPPE GIUFFRIDA, Attualità in tema di cardiopatia ischemica. Edizioni luigi pozzi - Roma. Copyright © Edizioni Luigi Pozzi s.r.l.
Numerous experimental studies, in addition to those reported in Figure 4, have demonstrated that stimulation of glucose oxidation both during and after ischemia can benefit the ischemic heart.¹⁵,¹⁶ By improving the coupling of glycolysis with glucose oxidation, proton production is decreased, resulting in decreased tissue acidosis and an improvement in cardiac efficiency. As a result, selective stimulation of glucose oxidation by trimetazidine may explain the anti-ischemic and anti-anginal effects of this agent by increasing the coupling between glycolysis and glucose oxidation. There is less proton production and acidosis, thus causing less angina pain and increasing the exercise time to angina and to electrocardiogram-ST alteration during exercise. These effects of trimetazidine are depicted in Figure 4 and summarized in Table 1. In summary,

**Effects of trimetazidine on cardiac metabolism**
- Inhibition of FFA β-oxidation
- Activation of pyruvate dehydrogenase
- Shift of metabolism from FFA to glucose

*Under ischemic condition, this results in:*
- Better cardiac energy via anaerobic ATP
- Less lactic acid, less acidosis, less angina
- Prolongation of exercise time to angina and to 1 mm ST depression in absence of hemodynamic effects

<table>
<thead>
<tr>
<th>Table 1</th>
<th>The effects of trimetazidine on cardiac metabolism.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trimetazidine inhibits fatty acid oxidation secondary to an inhibition of long-chain 3-ketoacyl CoA thiolase. This results in an improved coupling of glycolysis with glucose oxidation, less acidosis, and more anaerobic ATP production.</td>
<td></td>
</tr>
</tbody>
</table>

**Type 2 diabetes and cardiac metabolism**

Diabetes mellitus is an important predictor of future cardiovascular events in patients with and without ischemic heart disease.¹⁷,¹⁸ Patients with diabetes, but without overt CAD have a prognosis similar to CAD patients without diabetes, and patients with diabetes and CAD have a cardiovascular death rate double that of patients without diabetes and CAD.¹⁹ The diffuse distribution of atherosclerosis in patients with type 2 diabetes is related, in part, to the metabolic derangements of diabetes and, in part, to the clustering of different risk factors, such as elevated blood pressure, central obesity, and an altered lipid profile.

An important effect of diabetes at a myocardial level is the switch from carbohydrate oxidation to FFA and ketone oxidation. As observed in diabetic patients, elevated levels of acetyl-CoA and FFA inhibit PDH and pyruvate flux. In ischemia, these metabolic abnormalities result in an increased lactate release and are associated with calcium overload and, eventually, cell death leading to contractile dysfunction. In diabetic patients, levels of both FFAs and fatty acid esters are elevated. However, although FFA metabolism is elevated, esterified fatty acid is decreased. In addition to these changes in circulating FFAs, diabetes causes an increase in myocardial triglyceride content. The consequence is impaired ventricular performance, independent of blood pressure and significant CAD, which supports the existence of a condition termed ‘diabetic cardiomyopathy’.²⁰

Optimizing cardiac metabolism could become a new approach to the management of ischemic heart disease in diabetic patients. Clinical manipulations of metabolic substances are intended to shift the ischemic myocardium from FFA to glucose utilization.²¹ Studies conducted in isolated perfused hearts confirmed that a switch from FFA to glucose exerts favorable effects on the diabetic heart.²² In a prospective DIGAMI study (Diabetic Patients Receiving Insulin–Glucose Infusion during Acute Myocardial Infarction), the long-term mortality in diabetic patients admitted for acute myocardial infarction was reduced by 30% in 1 year with 24h glucose–insulin–potassium infusion followed by multidose insulin treatment. A meta-analysis of all of the trials on glucose–insulin–potassium infusion showed a 28% reduction in mortality at a 1-year follow-up, and this therapeutic regimen has been recommended for all diabetic patients suffering an acute myocardial infarction.²²

**Conclusion**

In conclusion, the inhibition of FFA oxidation with trimetazidine in CAD patients with or without diabetes improved cardiac metabolism at rest and during stress, and therefore, reduced the decrease in LV function caused by chronic hypoperfusion and repetitive episodes of myocardial ischemia. For this reason, in the recent ESC Guidelines on chronic ischemia, trimetazidine is recommended as an add-on drug acting by improving cardiac metabolism. In addition, trimetazidine should be considered for the treatment of patients with diabetes and CAD with or without LV dysfunction.
REFERENCES


Resolution of metabolic syndrome after bariatric surgery: a case report

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Abstract
There is a growing level of obesity in developed countries. The metabolic syndrome is a group of risk factors often present in the morbidly obese population that increases the risk of cardiovascular diseases. There has been great interest in the effect of bariatric surgery, particularly gastric bypass, in improving or resolving the metabolic syndrome in most patients. We report the case of a 48-year old woman with morbid obesity (body mass index, 40.5) who underwent a laparoscopic Roux-en-Y gastric bypass. At 12-months follow-up, the patient had lost 27% of excess body weight (body mass index, 29.7) with an improvement or resolution of her blood pressure, lipid profile, liver biochemistry, and glycemic control. ■ Heart Metab. 2014;63:29–32

Keywords: Angina; breathlessness; diet; gastric bypass; metabolic syndrome; obesity.

The metabolic syndrome encompasses a group of risk factors that increases the risk of developing cardiovascular disease, diabetes, and stroke. These risk factors include hyperglycemia, elevated blood pressure, dyslipidemia, and elevated waist circumference. Three out of five risk factors need to be present to make the diagnosis of metabolic syndrome according to the: (i) Joint Interim Statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; (ii) National Heart, Lung, and Blood Institute; (iii) American Heart Association; (iv) World Heart Federation; and (v) International Atherosclerosis Society and International Association for the Study of Obesity (Table I).'

The metabolic syndrome is highly prevalent in the morbidly obese and those referred for bariatric surgery. Numerous studies have reported improvements or resolution of diabetes, hypertension, and/or dyslipidemia in the early period after Roux-en-Y gastric bypass surgery, which may be due to a combination

1) Elevated waist circumference: >80 cm in Caucasian women (IDF and WHO).

2) Elevated triglycerides: >1.7 mmol/L (or receiving drug treatment for elevated triglycerides).

3) Reduced HDL-C: <1.3 mmol/L in women (or receiving drug treatment for reduced HDL-C).

4) Elevated BP: Systolic ≥130 mm Hg or diastolic ≥85 mm Hg (or receiving drug treatment for hypertension).

5) Elevated fasting glucose: ≥100 mg/dL or 5.5 mmol/L (or receiving drug treatment for elevated glucose).

Table I Criteria for the clinical diagnosis of metabolic syndrome'. The presence of any 3 of 5 risk factors constitutes a diagnosis of metabolic syndrome. After reference 1. Source: American Heart Association, Inc.
of weight-dependent and weight-independent mechanisms. Further, the benefits of bariatric surgery extend to a reduction in the future estimated cardiovascular disease risk.

We present the case of a morbidly obese patient who presented initially to the cardiology clinic with symptoms of angina. Her case highlights some of the previously documented medium-term benefits of bariatric surgery, but also discusses some of the outstanding issues to sustain the long-term benefit and the role the dietician plays in achieving long-term weight loss.

Case report
A 48-year-old woman was referred to the cardiology service in May 2011 for symptoms of exertional breathlessness and chest tightness. She had no chest pain at rest nor did she report any symptoms of orthopnea or paroxysmal nocturnal dyspnea. She did complain of mild peripheral edema. Her mobility was limited due to osteoarthritis of her right hip and she walked with the aid of a stick.

She had a number of comorbidities including morbid obesity (body mass index [BMI] of 40.5 and a waist circumference of 134 cm), hypertension, depression, and asthma. She was a smoker with a 10 pack/year history. Her blood tests revealed evidence of dyslipidemia and mildly deranged liver biochemistry (Table II). Her electrocardiogram was normal and the troponin test was negative. Her fasting blood glucose was elevated (7.5 mmol/L) and an oral glucose tolerance test revealed her blood glucose level to be 10.8 mmol/L, 2 hours after an oral glucose load, which confirmed the presence of impaired glucose tolerance. A liver ultrasound demonstrated marked echogenicity, which is in line with fatty liver disease. She met all the diagnostic criteria for the metabolic syndrome due to the presence of dyslipidemia, hyperglycemia, and hypertension on treatment as well as an elevated waist circumference, (Table I) and was considered at high risk for developing coronary artery disease.

A transthoracic echocardiogram was limited due to body habitus, but revealed normal biventricular function with no regional wall motion abnormalities or valvular heart disease. She proceeded to coronary angiography, which revealed mild-to-moderate

<table>
<thead>
<tr>
<th>Measure</th>
<th>Preoperative</th>
<th>Postoperative (1 year)</th>
<th>Reference range/targets (females)</th>
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</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>109</td>
<td>80</td>
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<tr>
<td>Body Mass Index</td>
<td>40.5</td>
<td>29.7</td>
<td>18.5 to 25.0</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>134</td>
<td>104</td>
<td>&lt;80 in Caucasians (WT/O/IDF criteria)</td>
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<tr>
<td>Total cholesterol (mmol/L)</td>
<td>6.3</td>
<td>5.4</td>
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<tr>
<td>Triglycerides (mmol/L)</td>
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<td>1.57</td>
<td>&lt;1.70</td>
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<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>1.16</td>
<td>1.32</td>
<td>&gt;1.30</td>
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<td>LDL cholesterol (mmol/L)</td>
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<td>3.36</td>
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<td>Blood pressure (mm Hg)</td>
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<td>112/68</td>
<td>&lt;140/90</td>
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<td>Fasting blood glucose (mmol/L)</td>
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<td>HbA₁c (mmol/mol)</td>
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<td>Albumin (g/L)</td>
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<td>42</td>
<td>40 to 52</td>
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<tr>
<td>Bilirubin (μmol/L)</td>
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<td>3</td>
<td>0 to 21</td>
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<tr>
<td>Alkaline phosphatase (IU/L)</td>
<td>146</td>
<td>72</td>
<td>35 to 129</td>
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<tr>
<td>Alanine transaminase (IU/L)</td>
<td>69</td>
<td>15</td>
<td>4 to 45</td>
</tr>
<tr>
<td>Gamma-glutamyl transpeptidase (GGT) (IU/L)</td>
<td>60</td>
<td>24</td>
<td>4 to 60</td>
</tr>
</tbody>
</table>

Table II Weight, waist circumference, lipid profile, blood pressure, glycemic control, and liver biochemistry pre and 1 year postbariatric surgery. The Joint International Diabetes Federation (IDF), National Heart, Lung and Blood Institute (NHLBI), and American Heart Association (AHA) criteria were used to make a diagnosis of the metabolic syndrome. According to these criteria (Table I), the presence of 3 out of 5 risk factors constitutes a diagnosis of metabolic syndrome. Our patients met 5 of the criteria preoperatively and only 1 criterion postoperatively confirming the resolution of metabolic syndrome postbariatric surgery. After reference 1. Source: American Heart Association, Inc.
atheroma in the left anterior descending artery (LAD), but the fractional flow reserve (FFR) was negative (Figure 1). The rest of her coronary system was clear. Therefore, a decision was made to manage her symptoms medically and advise her on lifestyle interventions.

Despite implementing a physical exercise regime and dietary adjustments, the patient’s weight remained static over the next 4 months. She continued to experience exertional breathlessness and reported increasing psychosocial stress and low self-esteem due to her weight. She was started on orlistat and lost 3 kg over a 6-week period, but had not achieved her target body weight after 3 months. Orlistat was therefore stopped and she was referred for bariatric surgery. After a full discussion of the risks and benefits, the patient elected to undergo a laparoscopic Roux-en-Y gastric bypass in April 2012. There were no postoperative complications and the patient was discharged on a high-protein, low-fat diet with vitamin, iron, and calcium supplementation.

The patient remained well, and by her 12-month follow-up, had lost 29 kg and demonstrated an improvement in her lipid profile, liver biochemistry, and hyperglycemia (Table II). She was keen to stop the amlodipine for her blood pressure as this was causing her troublesome peripheral edema. Her blood pressure remained within the correct range even after this was stopped, and, now, she only met one criterion from the list of metabolic syndrome criteria (Table I). Therefore, she was considered free from the metabolic syndrome. Most importantly for the patient, she reported an improvement in her cardiorespiratory status with no further symptoms of exertional breathlessness and chest pain and a subsequent improvement in her exercise tolerance and quality of life.

The patient reported that the involvement of the dietician in providing advice on meal frequency, fluid intake, dietary supplements, and behavioral changes significantly helped in the maintenance of weight loss after surgery. She was given detailed nutritional counseling preoperatively, and continued to visit the dietician at 3-monthly intervals postoperatively. She was provided with written information on the importance of lifestyle modifications and had regular telephone consultations to monitor adherence. All of these factors led to a positive effect on her weight-loss outcome and prevented weight regain after surgery.

The role of bariatric surgery in the metabolic syndrome

In our patient, there appeared to be a good outcome across a range of metabolic and functional parameters at 1-year follow-up. Some studies have reported that between 50% to 80% of patients referred for bariatric surgery may fit the criteria for having a diagnosis of metabolic syndrome. There are now multiple reports in the literature suggesting that after bariatric surgery there is either improvement in or resolution of a number of comorbidities including metabolic syndrome, diabetes, hypertension, and obstructive sleep apnea. Furthermore, evidence suggests that sustained and substantial weight loss after bariatric surgery is a powerful intervention to decrease the future risk of myocardial infarction and premature death in the morbidly obese. This has led some authors to suggest that bariatric surgery should not only be considered as surgery for morbid obesity, but also as surgery for metabolic disturbances.

While the short- and medium-term benefits of bariatric surgery on dyslipidemia, glycemic control, and hypertension are clear, there appear to be relatively few studies reporting long-term data on the effects of bariatric surgery on remission rates. Recent evidence found that over a 6-year median follow-up period after bariatric surgery, there was a 50% complete or partial type 2 diabetes mellitus remission rate. The STAMPEDE trial (Surgical Treatment And Medications Potentially Eradicate Diabetes Efficiently) recently
reported 3-year outcomes on the effects of bariatric surgery and intensive medical therapy on glycemic control. Patients who underwent bariatric surgery combined with intensive medical therapy had significantly better glycemic control compared with patients who received intensive medical therapy alone. There was also an improvement seen in body weight, use of glucose-lowering medications, and quality of life, which was sustained at the 3-year follow-up.  

There are also direct effects of profound weight loss on the heart, which are highlighted and discussed in the article by Oliver Rider in this issue.

Weight regain after bariatric surgery is a well-recognized clinical problem and has been linked to both surgical issues and lifestyle factors. A preclinical model of weight regain after Roux-en-Y gastric bypass suggested that around 20% of individuals may regain a large proportion of weight initially lost and reenter the category of morbid obesity. The dietician may play a key role in preventing weight regain after bariatric surgery through provision of practical nutrition knowledge, guidance, and encouragement of physical activity and promoting sustained lifelong changes in eating behaviors.

Conclusions

Obesity and its associated complications are an ever increasing clinical problem in developed countries. Bariatric surgery leads to an improvement in metabolic disturbances in addition to its effects on weight loss in the morbidly obese. The role of allied healthcare professionals, particularly the dietician, is important in maintaining weight loss after bariatric surgery and promoting lifelong changes in eating behaviors.

REFERENCES


Basic food composition: is it just sugar and fat?

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**Abstract**
Dietary guidelines for cardiovascular disease (CVD) prevention apply to the whole population as well as to people with CVD. They are based on the premise that reductions in the mean population serum low-density lipoprotein cholesterol and blood pressure will reduce the population risk of CVD. Guidelines recommend moderating the intake of fat so that it supplies between 25% to 35% of the energy with most of the fat derived from monounsaturated and polyunsaturated fatty acids with a restriction on saturated (<10% energy) and trans fatty acids (1% energy). This can readily be achieved by choosing lean cuts of meat especially chicken, reduced fat dairy foods, using vegetable oils such as olive oil and rapeseed oil for cooking in place of hard fats, and eating oily fish and nuts. It is generally advised that the intake of confectionary sugar, cakes, biscuits, and sugar-sweetened beverages should be restricted, but the intake of fruit, which is rich in sugar, and vegetables should be increased to five portions a day. Restricting salt intake to <6 g/day helps maintain normal blood pressure, but salt intake <3.5 g/day is associated with increased risk of death in patients with heart failure. Obesity contributes to the risk of CVD, therefore, maintaining a body mass index in the range of 20 to 25 kg/m² is a desirable, but often an unachievable, goal. Weight maintenance is determined by balancing energy intake with expenditure; however, restricting the intake of foods that provide most of the energy is a key to controlling body weight.  

**Keywords:** Blood pressure; cardiovascular risk; fat; salt; sugar.
Abbreviations
BP: blood pressure; CHD: coronary heart disease; CVD: cardiovascular disease; DG: dietary guidelines; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; MUFA: monounsaturated fatty acids; PHVO: partially hydrogenated vegetable oil; PUFA: polyunsaturated fatty acids; RCT: randomized controlled trial; SFA: saturated fatty acids; TC: total serum cholesterol

acids, to avoid foods containing industrial trans fats, and to reduce the intake of added sugars and salt. They have been translated into palatable food-based dietary guidelines, which are illustrated in Table I. This article reviews the scientific basis for these guidelines.

The dietary guidelines evidence for CVD prevention
The evidence supporting dietary guidelines is derived from observational data, which is mainly from prospective cohort studies as well as the effects of individual dietary components on surrogate CVD risk markers such as blood pressure (BP) and the serum lipid profile, but rarely from randomized controlled trials (RCTs) with clinical end points. Foods associated with an increased risk of CVD are red meat and sugar-sweetened beverages, and foods associated with a lower risk of CVD are whole grain cereals, nuts, fish, fruit and vegetables, and moderate intakes of alcohol. Milk and yogurt appear to be associated with a lower risk of CVD, but there is some uncertainty regarding cheese. Some of these associations are subject to residual confounding by other health-related behaviors and, therefore, may not be causal.

It would be an immense challenge to conduct a long-term trial of dietary modification on CVD because incidence rates are relatively low below the age of 60 years, thus requiring the recruitment of tens of thousands of people to change their diet for many years. It is impossible to conduct placebo-controlled, RCTs with diet, however, this has been done with some components such as vitamins, minerals, and long-chain n-3 polyunsaturated fatty acids (PUFA). RCTs of dietary antioxidant vitamins and selenium supplements (vitamin A, C, E, β-carotene, and selenium), homocysteine-lowering vitamins (folate acid, vitamin B6, and vitamin B12) show no effect on CVD outcomes. RCTs show that the risk of CVD may be increased by vitamin D and calcium supplementation, and that long-chain n-3 PUFA supplements may reduce the risk of cardiac death, but not CVD incidence or all-cause mortality in secondary prevention. Consequently, dietary supplements are not recommended for CVD prevention.

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Target</th>
<th>Food-based guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saturated fatty acids</td>
<td>&lt;10% energy</td>
<td>Choose lean cuts of meat, poultry, and chicken—avoid fatty meat and meat products. Choose reduced fat dairy produce, use monounsaturated oils for food preparation (i.e., olive oil, rapeseed oil)</td>
</tr>
<tr>
<td>Trans fatty acids</td>
<td>&lt;1%</td>
<td>Avoid fats containing partially hydrogenated vegetable oils</td>
</tr>
<tr>
<td>Total fat</td>
<td>25% to 35% energy</td>
<td>Avoid deep-fried foods, use oils and fat spreads sparingly</td>
</tr>
<tr>
<td>Oily fish</td>
<td>0.2 g of n-3 polyunsaturated fatty acids</td>
<td>At least 1 portion of oily fish/week: fresh tuna, mackerel, herring, pilchard, sardine, salmon</td>
</tr>
<tr>
<td>Whole grains</td>
<td>Encouraged, but amount not specified</td>
<td>Choose whole grain breakfast cereals, whole grain bread, brown rice, brown pasta</td>
</tr>
<tr>
<td>Added sugars</td>
<td>&lt;60 g added sugar</td>
<td>Restrict the intake of confectionery sugar, cakes, biscuits, and sugar-sweetened beverages</td>
</tr>
<tr>
<td>Fruit and vegetables</td>
<td>Potassium &gt;3.5 g/day</td>
<td>5 portions/day. One portion is 80 g, but fruit juice only counts as one portion</td>
</tr>
<tr>
<td>Salt</td>
<td>&lt;6 g/day</td>
<td>Do not add salt to food, choose foods with a reduced salt content</td>
</tr>
<tr>
<td>Energy intake</td>
<td>body mass index: 20 to 25 kg/m²</td>
<td>Balance energy intake with energy expenditure</td>
</tr>
</tbody>
</table>

Table I Dietary guidelines for cardiovascular disease prevention and their translation into food-based dietary guidelines.
Level and type of fat
High fat intake contributes to hyperlipidemia, which is the major underlying process in atherosclerosis. SFA (12 to 16 carbons long) and trans fatty acids increase total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) compared with carbohydrates, monounsaturated fatty acids (MUFA), or PUFA. Replacing fat with carbohydrates lowers high-density lipoprotein cholesterol (HDL-C) regardless of the glycemic index of the carbohydrate intake, but this may not be of any clinical significance. A 1 mmol/L decrease in LDL-C lowers CVD death and major events by 10% and 20%, respectively. Therefore, a 5% reduction in energy from SFA that would lower LDL-C by up to 0.3 mmol/L would be predicted to decrease the risk of fatal and non-fatal CVD by 3% and 6%, respectively. SFA intake has markedly decreased over the past 20 to 30 years in many countries including the UK, which is mainly due to the replacement of animal and hydrogenated fats with vegetable oils, and as a result, the average TC has decreased. SFA intake remains above the target of 10% in many Western countries, typically in the range of 11% to 14%, but further reductions in SFA intake may have only a modest impact on CVD.

Prospective cohort studies found that trans fatty acids, which result from industrial partially hydrogenated vegetable oils (PHVO), are associated with a 24% increased risk of CVD. PHVO were used to make margarine and shortenings for biscuits, cakes, and pastries. However, PHVO is now rarely used in Europe and the level of exposure in the United States has declined. In November 2013, the Food and Drug Administration issued a preliminary determination that PHVO are no longer recognized as safe. Nowadays, margarines contain fewer trans fatty acids and SFAs than butter.

Cohort studies show a lower risk of CVD when SFAs are replaced by PUFA, but not by refined carbohydrates or MUFA. They also show that replacing trans fatty acids with SFAs, MUFA, or PUFA decreases the risk of CVD.

Diet high in fat have the potential to increase energy intake because fats contain 9 kcal/g compared with 3.75 kcal/g for carbohydrates. Furthermore, meals high in fat (both saturated and unsaturated) promote postprandial lipemia that can result in the formation of atherogenic remnant particles, cause endothelial dysfunction and activate factor VII coagulant activity. Consequently, it is desirable to avoid meals high in fat. Furthermore, longer-term studies show that a lower fat intake does lead to a small 0.51 kg/m² reduction in body mass index.

Type of carbohydrate
Carbohydrates constitute the major source of food energy in most human diets. In the rural area of developing countries where CVD is still uncommon and serum TC concentrations are low, carbohydrates provide over 60% of the food energy mainly as starch from cereal crops such as rice, wheat, maize, or tubers. Prospective cohort studies in the United States found that high intake of sugar-sweetened beverages was associated with a greater risk of CVD. There has also been a substantial debate regarding the effects of fructose versus glucose, but a meta-analysis of metabolic feeding studies showed minimal differences between fructose and glucose: fructose slightly improved plasma glucose and body weight, but it slightly increased fasting and postprandial triglycerides. High intake of sugar-sweetened beverages may contribute to obesity rather than having a direct effect on CVD risk.

Prospective studies generally show fruit consumption to be associated with a lower risk of CVD. While fruit typically contains 10% to 20% sugar by weight, it also has vitamin C and potassium. Consequently, dietary guidelines encourage fruit consumption, but advocate restricting the intake of added sugars.

Salt
High salt intake is linked with BP and restricting salt intake lowers BP. For each 100 mmol reduction in sodium intake per day, a reduction in systolic/diastolic BP in hypertensive and normotensive subjects of 5.4/2.8 and 2.4/1.1 mm Hg, respectively can be expected. The impact of salt restriction on BP is greater in people over the age of 50, when renin concentrations are low, and in black Africans. To put these effects in context, a 20 mm Hg difference in systolic BP doubles the risk of CVD.

Salt is often added to food at the table or during food preparation, however, about 70% comes from processed food. The foods that are particularly high in salt are pickled foods such as ham, bacon, sausages, cheese, olives, some soups, and soy sauce (≥20% salt). Bread, which contains 1% to 2% salt, is also an important contributor to salt intake. However, it is
hard to measure salt intake from dietary records and it is more reliably estimated from measuring sodium output in urine: a urinary sodium excretion of 100 mmol/day is equivalent to a salt intake of 6 g/day. A recent meta-analysis reported a 2.59 relative risk of death\(^1\) in heart failure patients with a salt intake <3.5 g/day. Thus, the relationship between salt intake and blood pressure may be J-shaped with both low and high intakes having adverse effects on CVD.

Many people find it very difficult to follow low salt diets, in part, because the salt content of food is difficult to understand, and because people prefer salty food. The UK Food Standards Agency persuaded the food industry to gradually reduce the salt content of processed foods especially bread, cereals, sauces, and ready meals and then introduced a traffic light-labeling system for the salt levels in processed foods. Average salt intakes in the UK have decreased to 8 g/day and the average BP has fallen, which has contributed to the 55% decrease in CVD mortality that has occurred in the UK since 1997.\(^{18}\) Yet, salt intake remains high (>15 g/day) in some other European countries.

**Conclusion**
Dietary advice to prevent CVD has focused on reductions in SFA, sugar, and salt intake, but controlled studies where compliance to treatment is good only show modest changes in LDL-C and BP with a minimal impact on obesity. A more promising approach to CVD prevention is to modify the overall dietary pattern as in the DASH (Dietary Approaches to Stop Hypertension)\(^{19}\) and OMNINHEART (Optimal Macronutrient Intake Trial to Prevent Heart Disease)\(^{20}\) trials, which were designed to mimic dietary patterns associated with a lower risk of CVD.\(^{21}\)

**REFERENCES**

The effects of bariatric surgery on the heart

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Obesity is associated with an increased cardiovascular mortality rate, and an even greater risk is associated when the body mass index (BMI) exceeds 35 kg/m².1 As obesity is now a global problem affecting virtually all ages and socioeconomic groups, it has become a major contributor to the global burden of cardiovascular disease. Structural and functional changes in the cardiovascular system occur in response to obesity including; ventricular hypertrophy, diastolic dysfunction, reduced myocardial energetics,2 and aortic stiffness,3 all of which are associated with adverse cardiovascular risk.4-7 In addition to these structural changes, obesity is associated with the metabolic syndrome, hypertension, insulin resistance,8 chronic subacute inflammation9 and activation of the renin-angiotensin system10 resulting in a proatherosclerotic environment, further increasing cardiovascular risk (Figure 1).

Fig. 1 The effects of obesity and bariatric surgical weight loss on the cardiovascular system.
The effects of bariatric surgery

Although successful in the short-term, the traditional treatments to achieve weight loss such as diet, lifestyle, and behavioral therapy have proven relatively ineffective in the long-term to achieve either sustained weight loss or improvement in the cardiovascular risk factor profile, and are especially ineffective in morbidly obese patients (BMI >40 kg/m²). This led to the development of specific surgical treatments (i.e., bariatric surgery) to treat morbid obesity and its comorbidities.

Surgical weight loss has been shown to have beneficial effects on cardiac geometry with reduced ventricular mass and cavity size as early as 3 months following bariatric surgery, with additional improvements in aortic elastic function and cardiac high-energy phosphate metabolism accompanying sustained reduction in fat mass. In addition to the positive effects on cardiovascular structure and function, both exercise capacity and clinical symptoms also improve after bariatric surgery. In addition, over a 3-year period, bariatric surgery has been shown to be superior to intensive medical therapy for the treatment of diabetes. Evidence now suggests bariatric surgery improves subclinical cardiac dysfunction and, as a result, has the potential to reverse obesity-related cardiomyopathy. The mechanisms by which bariatric surgery achieves improved cardiovascular physiology are likely to include reduced circulating volume, decreased inflammation, and modification of adipokines and gut hormones (Figure 1). The ability of bariatric surgery to reverse the components that comprise the metabolic syndrome is illustrated in the case report by Rahul Mukherjee in this issue.

The obesity paradox

Although obesity is a major risk factor for the development of congestive heart failure, obesity itself is associated with better survival in patients with manifest cardiac failure. The reasons for this “obesity paradox” are not well understood, but are extremely important given the high prevalence of both obesity and heart failure in the general population. Given the survival advantage that obesity confers to heart failure, there is now a genuine question as to whether bariatric surgery in this setting would be beneficial or remove the survival advantage conferred by obesity. While positive reverse cardiovascular remodeling and improved survival in the general population occurs with bariatric surgery, whether or not these beneficial effects can be achieved in a heart failure patient remains unknown. Given the current lack of guidelines on weight management in heart failure, answering this question is of great clinical importance and further studies are needed.

Conclusion

There is now clear evidence that bariatric surgery confers beneficial effects to the cardiovascular system. However, these benefits need to be weighed against the possible increase in operative risk in obese subjects and especially in patients with overt obesity cardiomyopathy, despite the fact that this population is likely to gain the most benefit from weight loss. Although it is likely that bariatric surgery will have long-term benefits in preventing and treating obesity-related cardiovascular disease, to date, no randomized studies have assessed the effects of bariatric surgery in either reducing the incidence of heart failure and myocardial infarction or reducing mortality in patients with established heart failure.

REFERENCES

**Fibroblast growth factors (FGFs)**

FGFs are secreted glycoproteins, which are localized to the extracellular matrix by heparin sulfate proteoglycans. The activity of various heparinases, proteases, and FGF-binding proteins will release FGFs from the extracellular matrix, and then free FGFs can activate cell surface FGF receptors. FGF2 is the most characterized FGF and important paracrine factor involved in the development of cardiac hypertrophy.

**Insulin-like growth factors (IGFs)**

IGFs (IGF-1 and IGF-2) share sequence similarity with insulin. IGF-1 is an important mediator of the effects of growth hormone (GH). Secretion of GH increases IGF-1 secretion from the liver and local tissues, which, in turn, stimulates systemic body growth. In the heart, IGF-1 is an important regulator of physiological growth/physiological hypertrophy. Furthermore, IGF-1 may be implicated in heart failure where its circulating levels are decreased.

**Monounsaturated fatty acids (MUFAs)**

MUFAs are fatty acids that contain only one double bond in their carbon backbone. Oleic acid is one of the most important MUFAs because it circulates at the highest concentration in our body and is critical for energy metabolism.

**Peroxisome proliferator-activated receptors (PPARs)**

PPARs are members of the ligand-activated nuclear receptor superfamily. In mammals, three distinct PPAR isofoms have been identified (PPARα, PPARγ, and PPARδ) with differential tissue distributions. PPARs regulate the expression of various enzymes involved lipid metabolism by forming heterodimers with retinoid X receptors and binding to PPAR response elements in the promoter region of target genes.

**Polyunsaturated fatty acids (PUFAs)**

PUFAs are fatty acids that contain more than one double bond in their carbon backbone. The essential fatty acids, alpha-linolenic acid (omega-3 fatty acid) and linolenic acid (omega-6 fatty acid) represent two of the most important PUFAs as they cannot be synthesized endogenously in our bodies.

**Sirtuin proteins (SIRTs)**

SIRT proteins are orthologues of the silent information regulator 2 (SIR2) gene family, which is conserved from bacteria to humans. SIRTs are either class II histone deacetylases/NAD⁺-dependent lysine deacetylases (SIRT1, -2, -3, -5, -7) or ADP-ribosyltransferases (SIRT4, -6) with varying subcellular localization. SIRTs have been implicated in regulating lifespan/longevity in lower organisms. They are also important regulators of a variety of processes in mammalian cells including signal transduction, cellular transport, gene transcription, and metabolism.

**Trimethylamine-N-oxide (TMAO)**

TMAO is an organic amine oxide, which is formed from the oxidation of trimethylamine and hydrogen peroxide via the catalytic activity of flavin monoxygenase. TMAO may act as an important osmoregulatory compound affecting buoyancy and potentially protecting protein function under high pressure in fish. Recent studies in animals and humans also suggest that TMAO may act as a proatherogenic compound, and elevated TMAO levels are positively associated with increased cardiovascular risk in both rodents and humans.
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