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It is well established that obese individuals are at an increased risk of developing cardiovascular disease. As a result, the dramatic increase in the incidence of obesity worldwide will have a profound impact on the severity and incidence of heart disease. Indeed, as a risk factor for heart disease, obesity in the 21st century is what tobacco was in the 20th century. In tackling the problem of obesity, it is obviously important to try to decrease both the incidence and severity of obesity. In addition, it is also critical to gain a better understanding of how obesity contributes to the development of heart disease, and to develop and optimize treatments that lessen its impact on heart disease. Although patients with obesity have an increased risk for ischemic heart disease, a significant proportion of these patients will develop heart failure independent of ischemia. This edition of Heart and Metabolism addresses the important topic of obesity, highlighting the mechanistic links between obesity and heart disease, and therapeutic strategies for diagnosing and treating heart disease in the obese individual.

A number of direct changes to the myocardium can contribute to the development of cardiac dysfunction in the patient with obesity. These include a link between excessive rates of fatty acid β-oxidation in the heart and alterations in cardiac function. In the Basic Article, E. Dale Abel discusses the effects that obesity exerts directly on the alterations in fatty acid metabolism in the heart, which contributes to the development of insulin resistance. Potential mechanisms responsible for accelerated cardiac fatty acid oxidation rates in obesity are also discussed. This raises the possibility of targeting fatty acid metabolism directly as an approach to treating heart disease in obesity.

Brown adipose tissue (BAT) differs from white adipose tissue in that it is rich in mitochondria. Although long known to be important in metabolic and temperature control in rodents, the role of BAT in controlling metabolic rates in humans has not been obvious, because it was believed that BAT stores were very small in humans. However, the recent discovery that BAT activity can be detected in a substantial proportion of the adult population has generated a renewed interest in the study of this tissue. The New Therapeutic Approaches article by Peter Butler and colleagues also highlights the potential of stimulating BAT metabolism as a future therapeutic approach for treating obesity and insulin resistance. Measuring BAT content in humans has been difficult, but the Metabolic Imaging article by Kirsi Virtanen and Pirjo Nuutila provides some interesting data showing that positron emission tomography is a highly sensitive, noninvasive tool for the in-vivo imaging of BAT in humans, providing unique information on the basic function and physiology of BAT.

Important BAT proteins involved in the control of metabolic rates are the mitochondrial uncoupling proteins (UCPs), which have long been known to control metabolic rates and body temperature in BAT of rodents. The UCPs dissipate the mitochondrial membrane potential, resulting in energy expenditure directly towards heat production as opposed to energy production. More recently, UCPs have emerged as important determinants of metabolic rate in humans. This not only occurs in BAT, but also via the expression of different UCP isoforms in other tissues, such as...
skeletal muscle. The Refresher Corner article by Frédéric Bouillaud provides an excellent review of the role of UCPs in physiology, and the recent interest in these proteins as potential targets in the treatment of obesity.

The contribution of obesity to cardiovascular disease necessitates early disease detection and prompt intervention in this high-risk group. However, as highlighted in the Case Report by Ian Webb and Michael Marber, accurate assessment of symptoms can be challenging at times, because of the presence of several comorbidities. An example of this complexity is presented in the case report of a patient with obesity who was under multidisciplinary care for symptoms of breathlessness; many of these issues arose in this patient. The Hot Topics article by Alda Huqi also reviews a number of clinical trials showing that most of the reduction in cardiovascular mortality and morbidity reported in recent years has been attributed to preventive measures, but that these same preventive measures, when individually tested in high-risk subgroups of patients, often fail to improve clinical outcomes. The Main Clinical Article by Jennifer Logue and Naveed Sattar also highlights the complexity of the relationship between obesity and heart disease. Although an association between obesity and increased heart disease is well established, there exists an “obesity paradox” in which there is a greater survival among obese patients with cardiac failure. The authors describe the phenomenon and discuss possible factors that may be responsible for this apparent paradox.

With the epidemic of obesity in our society, this edition of *Heart and Metabolism* is a timely publication, with a number of articles discussing ways in which to “Tackle Obesity”. Failure to address these important issues will almost assuredly contribute to an increase in the incidence of heart disease in the world.

*see glossary for definition of this term.*
Free fatty acid oxidation in insulin resistance and obesity

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Abstract

The growing worldwide epidemic of obesity and diabetes portends a significant increase in cardiovascular disease. Obesity is associated with insulin resistance, and there is growing evidence that these conditions independently increase the risk of heart failure. Changes in myocardial substrate utilization develop in obesity and insulin resistance, and are characterized by increased fatty acid oxidation and utilization, and decreased glucose utilization. This paper will review the evidence for altered myocardial fatty acid utilization in obesity and insulin resistance, review mechanisms that are responsible, and discuss the relative contributions of systemic and myocardial insulin resistance in the regulation of fatty acid utilization in the heart.

Heart Metab. 2010;48:5–10.

Keywords: Fatty acid oxidation, insulin resistance, myocardial substrate utilization, obesity

Introduction

Recent statistics indicate an inexorable increase in the prevalence of obesity and insulin resistance in the developed world and emerging economies. These demographic changes are fueling an increase in the incidence of obesity-related disorders such as cardiovascular disease (CVD), diabetes, and sleep-disordered breathing [1,2]. The clustering of obesity, insulin resistance, and increased CVD risk has been termed the metabolic syndrome, and is defined by a clustering of abdominal obesity, increased triglyceride, decreased high-density lipoprotein cholesterol, glucose intolerance, and hypertension [3]. The increased prevalence of CVD in individuals with the metabolic syndrome is multifactorial and results from increased atherosclerosis, leading to: increased coronary artery disease (CAD) and myocardial ischemia; hypertension – an important risk factor for left ventricular hypertrophy and heart failure; increased hypercoagulability; sleep-disordered breathing that increases the risk of cardiac hypertrophy and atrial fibrillation; and glucose intolerance and diabetes, which amplify the aforementioned risks and which may have direct adverse consequences on the myocardium [1]. Obesity and diabetes are also independently associated with heart failure, even after adjusting for underlying CAD, and potential mechanisms have been reviewed in recent years [4,5]. This review will focus on the potential role of altered myocardial fatty acid utilization.

Pathophysiology of insulin resistance

Although genetic predisposition to insulin resistance and obesity exists, it is widely accepted that a major contribution to the increasing prevalence of obesity and insulin resistance is caloric excess and an increasingly sedentary lifestyle [2]. As body weight increases,
there is expansion of the adipose tissue mass, particularly visceral adipose tissue. Insulin signaling is downregulated in adipose tissue, skeletal muscle, and the liver [6]. Because of the central role of insulin signaling in suppressing lipolysis, insulin resistance in adipose tissue is associated with increased release of free fatty acids, which in turns fuels increased hepatic generation of triglycerides. Expansion of adipose tissue is associated with increased release of adipokines such as leptin, and various inflammatory cytokines such as tumor necrosis factor-α. Moreover, there is reduced release of adiponectin. Insulin resistance also reduces adipocyte glucose transport, which might directly lead to increased release of the adipokine, retinol binding protein 4. These humoral and metabolic changes have all been implicated as potential mediators of changes in myocardial fatty acid utilization [1]. Insulin resistance also develops in skeletal muscle and liver. Several mechanisms are responsible for hepatic and muscle insulin resistance. These include: (1) lipotoxicity, arising from increased lipid deposition in these organs, which impairs insulin action as a consequence of increased accumulation of triglycerides and lipid intermediates such as ceramide and diacylglycerol (DAG) [7]; (2) increased activation of nutrient-sensing pathways such as the hexosamine biosynthetic pathway, which directly impairs insulin signaling [8]; (3) increased activation of inflammation-mediated signaling cascades such as Toll-like receptor (TLR) signaling, and jun N-terminal kinase (JNK) signaling pathways [9]; (4) mitochondrial dysfunction, which has also been implicated in insulin resistance, although there is controversy regarding whether or not these are primary or secondary changes [10]. Many of these changes may also occur in cardiac muscle, and could potentially contribute to changes in cardiac metabolism. Although accumulating evidence suggests that myocardial insulin resistance develops in obesity and diabetes, as characterized by impaired insulin-stimulated glucose utilization, evidence from animals and humans suggests that proximal insulin signaling in the heart might be maintained, meaning that certain intracellular signaling pathways might actually be hyperactivated in the heart as a result of the hyperinsulinemia that inevitably accompanies systemic insulin resistance [11,12].

Myocardial fatty acid utilization in obesity and insulin resistance: insights from human and animal studies

The overwhelming majority of studies in this area have been performed in individuals or animal models of type 2 diabetes; they have been the subject of many review papers [1,4,13]. However, some recent studies have examined fatty acid utilization in humans and animals with obesity before the onset of significantly impaired glucose tolerance or diabetes. In a study of obese and insulin-resistant females, Peterson and colleagues [14] observed increased rates of myocardial fatty acid uptake, utilization, and oxidation, and increased myocardial oxygen consumption (mVO₂), which increased in proportion to body mass index or to the degree of glucose intolerance. Independent studies in obese individuals have also described an association between obesity and increased myocardial concentrations of triglyceride [7]. Buchanan et al [15], reported that myocardial fatty acid oxidation and mVO₂ were increased and cardiac efficiency was decreased in 4-week-old ob/ob and db/db mice (both of which develop obesity and insulin resistance, on the basis of leptin deficiency or resistance, respectively) at a time when these animals were obese and before the onset of hyperglycemia. Recent studies in rodents placed on high-fat and high-carbohydrate diets have also revealed increased myocardial fatty acid uptake and rates of fatty acid oxidation that precede the development of significant obesity or glucose intolerance [12,16]. Taken together, the findings of these studies support the conclusion that increased myocardial fatty acid utilization is a characteristic response of the heart to obesity or caloric excess and occurs independently of or before the onset of diabetes or impaired glucose tolerance.

Molecular mechanisms

PPARα signaling, glucose uptake, and fatty acid uptake

The classical view of the mechanism leading to increased fatty acid oxidation in obesity has been that obesity increases circulating concentrations of fatty acids, which in turn activates PPARα. Indeed, pharmacological activation of PPARα or transgenic overexpression of PPARα in the heart increases myocardial fatty acid oxidation [17,18]. As summarized in Figure 1, PPARα transactivates most genes involved in myocardial fatty acid utilization, including those involved in fatty acid uptake at the sarcolemma, generation of fatty acyl coenzyme A (CoA), mitochondrial uptake of fatty acyl CoA, and mitochondrial β-oxidation. An important regulatory node is mitochondrial fatty acyl CoA uptake via carnitine palmitoyl transferase-I (CPT-I), which is under allosteric inhibition by malonyl CoA. Steady-state concentrations of malonyl CoA are determined by the balance of synthesis by acetyl CoA carboxylase and degradation via malonyl CoA decarboxylase. Acetyl CoA carboxylase is inhibited by AMP kinase (AMPK), and malonyl CoA decarboxylase is a target of PPARα.
Thus activation of AMPK or PPARα would decrease malonyl CoA concentrations by decreasing synthesis or by increasing malonyl CoA degradation. Decreasing concentrations of malonyl CoA will increase CPT-I activity. Recent studies have suggested that PPARα activation might not be an early event leading to increased fatty acid utilization in the heart in obesity, but may be a later event that sustains the increase. Four-week-old ob/ob and db/db mice exhibit significantly increased fatty acid oxidation before any increase in the expression of PPARα-regulated target genes, the levels of which increase only as the animals age [15]. Moreover, after short-term high-fat feeding, an increase in fatty acid oxidation was clearly evident as early as 2 weeks, and occurred in the absence of significant changes in the expression of PPARα target genes and even in the absence of changes in circulating concentrations of free fatty acids and triglycerides. Evidence for activation of PPARα target genes was seen only after 5 weeks of high-fat feeding, which would be predicted to increase malonyl CoA as a result of disinhibition of acetyl CoA carboxylase activity [19]. Moreover, increased concentrations of malonyl CoA, and normal CPT-I activity, were noted in the hearts of db/db mice [20]. An additional mechanism that might drive fatty acid utilization early in the evolution of high-fat feeding or obesity-related cardiac dysfunction is increased plasma membrane translocation of the fatty acid transporter, CD36. This was recently described in the hearts of db/db mice, and in Zucker (fa/fa) rats and rats fed a high-fat diet [16,20,21]. It is interesting to note that CD36 translocation in the heart is stimulated by insulin signaling in an Akt/PKB-dependent manner. It is well established that insulin acutely suppresses fatty acid oxidation, thus the simultaneous increase in CD36 translocation might seem to be paradoxical. However, in light of a recent report that most of the fatty acids that are oxidized in the heart arise from the endogenous triacylglycerol (TAG) pool [22], the possibility exists that, under physiological conditions, CD36 translocation could be a mechanism for increasing fatty acid utilization in the heart.
conditions, insulin may serve to replenish the cardiac TAG pool. It is further postulated that, under conditions of chronic hyperinsulinemia, because proximal insulin signaling to Akt remains intact in the heart in the evolution of diet-induced obesity, the associated hyperinsulinemia could increase CD36 translocation to the plasma membrane, thereby contributing to further expansion of the TAG pool and increased likelihood of accumulation of potential toxic intermediates of lipid metabolism.

**Mitochondrial mechanisms**

Recent studies in mouse models of obesity and insulin resistance such as ob/ob, db/db, and UCP-DTA (Uncoupling Protein-Diphtheria Toxin A) transgenic mice suggest that mitochondrial uncoupling accompanies the metabolic changes that develop in the heart [23–25]. It is not known if mitochondrial uncoupling contributes to the changes in fatty acid metabolism per se, but it might contribute in part to the associated increase in mV̇O₂ and reduction in cardiac efficiency. A proposed mechanism for increased mitochondrial uncoupling in obesity and insulin resistance is an increase in mitochondrial superoxide generation that leads to activation of uncoupling proteins. Increased production of reactive oxygen species (ROS) is probably the consequence of an imbalance between increased generation of reducing equivalents from β-oxidation and impaired function of the electron transport chain [23,24]. A recent study using atrial appendages derived from humans with diabetes also demonstrated mitochondrial dysfunction and increased ROS generation. The strongest data to support mitochondrial uncoupling have been obtained in mouse models of obesity and type 2 diabetes. Hyperglycemia alone might not be sufficient to induce mitochondrial uncoupling, as we and others have observed no evidence for mitochondrial uncoupling or increased ROS generation in mitochondria of models of type 1 diabetes [26]. Thus ROS-induced mitochondrial uncoupling might be unique to diabetes that is associated with insulin resistance. Of interest, genetic disruption of insulin signaling in cardiomyocytes leads to mitochondrial dysfunction that is characterized by increased ROS generation and mitochondrial uncoupling [27].

**Myocardial insulin resistance**

Impaired myocardial insulin-stimulated glucose uptake has been described in many studies of humans and animal models with obesity and insulin resistance [1,28]. As discussed above, this might be the result of decreased translocation of GLUT4, leading in turn to increased fatty acid utilization. Although insulin signal transduction might be relatively preserved at early stages, studies performed in some models of diet-induced obesity and in genetic models of obesity and insulin resistance (often with associated diabetes), suggest that insulin signal transduction might also be impaired [29–32]. Thus the question arises regarding the direct effects of myocardial insulin resistance on myocardial fatty acid utilization. The best data have come from mouse models with genetic defects in insulin action that are restricted to cardiomyocytes. These models are not confounded by secondary metabolic consequences such as altered circulating concentrations of lipids, glucose, insulin, or cytokines, which could have a secondary effect on cardiac metabolism. We have examined fatty acid metabolism in mice with genetic deletion of insulin receptors (cardiomyocyte-selective insulin receptor knockout [CIRKO]) and in mice that express a dominant negative phosphatidylinositol 3-kinase transgene (PI3K) [33,34]. In both these models, impaired insulin signaling to PI3K is associated with decreased rates of myocardial fatty acid oxidation that is attributable to reduced expression of PPARα and β-oxidation genes, and mitochondrial dysfunction. In CIRKO mice, we also confirmed, using proteomic analyses, that the mitochondrial content of fatty acid oxidation proteins was reduced. This contrasts with models of type 1 diabetes, which are also insulin deficient, but in which there is an increase in mitochondrial fatty acid oxidation proteins. Thus impaired myocardial insulin signaling directly regulates the capacity for mitochondrial fatty acid oxidation proteins. Impaired myocardial insulin signaling also demonstrated increased ROS generation and mitochondrial dysfunction and increased ROS generation. The strongest data to support mitochondrial uncoupling have been obtained in mouse models of obesity and type 2 diabetes. Hyperglycemia alone might not be sufficient to induce mitochondrial uncoupling, as we and others have observed no evidence for mitochondrial uncoupling or increased ROS generation in mitochondria of models of type 1 diabetes [26]. Thus ROS-induced mitochondrial uncoupling might be unique to diabetes that is associated with insulin resistance. Of interest, genetic disruption of insulin signaling in cardiomyocytes leads to mitochondrial dysfunction that is characterized by increased ROS generation and mitochondrial uncoupling [27].

**Conclusion**

An increase in myocardial fatty acid oxidation is an early and consistent finding in obesity and insulin resistance. The mechanisms for the increase in fatty acid utilization are multifactorial, and are summarized in Figure 2. Recent studies have highlighted an important role for changes in glucose utilization as a potential initial inciting event that leads to increased fatty acid oxidation. In addition, preservation of proximal insulin signaling (despite increased concentrations of DAG) promotes plasma membrane translocation of CD36. Later changes are sustained
Obesity and myocardial fatty acid oxidation

Figure 2. Mechanisms leading to increased myocardial fatty acid oxidation in insulin-resistant states. In the evolution of diet-induced obesity, or in type 2 diabetes, hyperinsulinemia activates insulin receptors (IR) and Akt (protein kinase B), leading to increased plasma membrane translocation of CD36, which leads to increased fatty acid uptake. Decreased expression and translocation of glucose transporter-4 (GLUT4) in insulin resistance leads to decreased glucose uptake and decreased glycolysis, which further increase fatty acid utilization. Reduced GLUT4 translocation precedes significant downregulation of insulin signal transduction to Akt. Mechanisms for reduced GLUT4 translocation are incompletely understood. Increased lipid availability activates PPARα, which leads to increased expression of proteins involved in fatty acid utilization, and increased pyruvate dehydrogenase kinase-4 (PDK4), which increase fatty acid oxidation (FAO) and decrease glucose oxidation, respectively. Increased FAO is associated with increased myocardial oxygen consumption (mVO₂). As insulin resistance progresses and diabetes ensues, reactive oxygen species (ROS)-mediated mitochondrial uncoupling develops, which further increases mVO₂, decreases ATP generation, and decreases cardiac efficiency. 1–IV, Mitochondrial electron transport chain complexes I–IV; Akt-p, phospho-Akt/protein kinase B; ANT, adenine nucleotide translocase; CoA, coenzyme A; TAG, triacylglycerol; UCP, uncoupling proteins 2 and 3.

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Obesity and mortality: summary of best evidence with explanations for the obesity paradox

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Abstract

The link between obesity and increased risk of mortality is well established. However, those who are obese have greater survival when they have chronic diseases such as rheumatoid arthritis or cardiac failure; this is known as the “obesity paradox”. The obesity paradox is most probably attributable to obese individuals being more susceptible to milder forms of disease than normal-weight individuals, although other mechanisms may also operate. The benefits of weight loss in the general population are also unclear, as some study participants also lose weight through disease. Further work is required to help guide weight recommendations in both healthy individuals and those with chronic diseases.

Keywords: Cardiovascular disease, death, mortality, obesity, obesity paradox

The patterns of association between adiposity and increased risk of death in the general population are now well established and exemplified by two recent powerful studies. A meta-analysis of 57 studies involving 894,576 participants, the Prospective Studies Collaboration [1], recently showed that all-cause mortality is lowest at body mass index (BMI) 22.5–25 kg/m², after adjustment is made for age, sex, and smoking status, and excluding deaths in the first 5 years of follow-up. For each 5 kg/m² increase above BMI 25 kg/m², there was a 39% greater mortality from ischemic heart disease, 39% from stroke, 116% from diabetes, 59% from renal disease, and 82% from liver disease. These results were broadly similar to results from the European Prospective Investigation into Cancer and Nutrition [2], which followed 359,387 participants for approximately 10 years and adjusted for key potential confounders of educational attainment, smoking, alcohol, physical activity, and height. They found the lowest risk of death to be at BMI 25.3 kg/m², with a 28% increase in mortality at BMI 30–34.9 kg/m² and 106% at BMI >35 kg/m², compared with BMI 23.5–25 kg/m².

The obesity paradox

The link between obesity and mortality in the general population is well established; however, there is conflicting evidence in disease states, with obesity seemingly having a protective effect against mortality; this is known as the “obesity paradox”. For example, in a meta-analysis of studies with a total of 28,209 patients with cardiac failure [3], patients with a BMI in the overweight and obese categories had 16% and 27%, respectively, lower all-cause mortality during 2.7 years of follow-up than patients in the normal weight (BMI 18.5–24.9 kg/m²) category. A similar pattern was observed for patients with coronary artery disease [4]: in the follow-up of 250,152 such patients, even after adjustment for confounding factors, the
overweight category had a 13% lower mortality over 3.8 years than the normal-weight group, with no differences in mortality seen in the obese (BMI 30–34.9 kg/m²) and severely obese (BMI ≥35 kg/m²) categories compared with normal-weight.

In rheumatoid arthritis, a near-linear relationship exists between increasing BMI and lower mortality, with the effect existing even in severe obesity. In a prospective cohort of 779 patients, the mortality rate over 4.4 years associated with a BMI >30 kg/m² was 66% lower than that in patients with BMI 20–24.9 kg/m², even after adjustment for smoking, duration of disease, and medication [5]. Survival after non bariatric general surgery was also increased in the obese: a prospective cohort of 118,707 patients showed a 31% lower mortality for those with BMI 30.1–35 kg/m² and 41% lower mortality with BMI >35 kg/m² compared with individuals of normal weight [6].

The two main explanations for the obesity paradox are residual confounding or “selection” bias, and a possible protective effect of obesity against the complications of cachexia states. Selection bias/residual confounding is probably the major factor in all the studies reviewed above. This is shown most clearly in the rheumatoid arthritis study, in which the positive association between baseline BMI and improved survival disappeared on adjustment for severity of disease and comorbidity [5].

In the heart failure meta-analysis, there were many differences between obese and non obese groups that would bias survival in the obese group: these included younger age (6.4 years), greater left ventricular ejection fraction, 11% fewer current smokers, 10% fewer with a previous myocardial infarction indicating a possible alternative pathophysiology, and 15% more who were prescribed B-blockers [3]. In the general surgery cohort, obese categories were also younger, less likely to smoke, less likely to have had an emergency procedure, more likely to be receiving antihypertensive drugs that may have a cardioprotective effect during and after surgery, and had far less preoperative non intentional weight loss [6]. In other words, although obesity can lead to earlier development of diseases, it is of a different characteristic (often more benign) than that in a leaner individual. For lean individuals to develop major diseases such as heart failure, major pathophysiological factors that are more aggressive in nature must be prevalent, in turn explaining earlier death in such individuals. Attempts are being made to adjust for some of these factors in epidemiological studies, but it is not possible to do so completely.

A possible protective effect of obesity against the complications of cachexia states is, of course, another possible explanation for the obesity paradox in certain conditions, but there are currently no data to prove this direct link. It is well known that disease states, severity, and cachexia are all linked, with cardiac cachexia in heart failure [7], rheumatoid cachexia [5], and cancer cachexia [8] being prime examples. It seems plausible that having access to large adipose stores during acute or chronic illness helps avoid the complications of cachexia. There is also some early in-vitro evidence that adipose tissue itself may have an effect on the immune system [9] that may be beneficial during severe illness; however, that has not been borne out in vivo, and is beyond the scope of this review.

Obesity treatment and mortality

The evidence for the effect of weight-loss treatments on mortality is surprisingly poor, given the importance of this topic and the current recommendations for weight loss [10]; this is because of the considerable difficulties associated with study design. Most obesity treatments only produce modest weight loss – in the region of 5 kg – and thus large sample sizes and long-term follow-up would be required. To be able to attribute any differences in mortality to weight loss would require a pure obesity treatment; obesity drugs may have effects on mortality that are independent of weight loss [11]. Simply looking at weight change in large cohort studies has produced results that are in disagreement with current recommendations: they show that weight loss is associated with increased mortality [12,13]. However, these non interventional studies dealing with small amounts of weight change are heavily confounded by the effects of non intentional weight loss in disease states.

Studies involving bariatric surgery have the benefit of large weight loss that would far exceed any disease-related non intentional weight loss (≥20 kg); however, large randomized trials are not financially viable, and the resulting studies have the bias of those in the cohort who elected to have surgery, versus those that chose not to. Nevertheless, two large studies have been published showing a beneficial effect on mortality of weight loss from bariatric surgery. The Swedish Obese Subjects study, a prospective cohort study of 2010 patients having a variety of bariatric surgery operations compared with 2017 patients having non surgical obesity management, showed a 29% reduction in mortality in the operated group over 10.9 years of follow-up [14]. A similar retrospective cohort study matched, for weight, 9,949 patients having gastric bypass with a control group from among driving license applicants, and showed a 40% reduction in mortality among the operated group over 7 years, with 49% fewer cardiovascular deaths and 60% fewer cancer deaths [15]; however, weight was self-reported by driving license applicants, and the death data were from death certification, so the accuracy of the data used could not be guaranteed.
Key points

- In the general population, risk of death increases with a body mass index \( >25 \text{ kg/m}^2 \).
- In studies of patients with disease such as heart failure and rheumatoid arthritis, increasing body mass appeared to be associated with decreased mortality – the “obesity paradox”.
- The obesity paradox may be explained by overweight and obese individuals getting symptomatic, but less severe, forms of disease at an earlier age than normal-weight individuals, biasing their survival.
- The effects of intentional weight loss on risk of death are not clear, as studies have been confounded by non intentional disease-related weight loss.
- Large-scale weight loss with bariatric surgery does appear to have a beneficial effect on mortality, with a reduction in mortality of between 27 and 40% compared with similarly obese individuals choosing not to have surgery.

Summary

The best available evidence supports an adverse effect of obesity on mortality. However, there is little evidence available, other than in bariatric surgery, that reducing weight with obesity treatments decreases mortality rates. Until there is an improvement in data about the long-term benefits or otherwise of weight loss in those already obese, efforts should continue to focus on the prevention of obesity, and on the weight maintenance of those already overweight and obese.

*see glossary for definition of this term.*

REFERENCES

Functional imaging of brown adipose tissue

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Abstract

Human brown adipose tissue (BAT) has been found to be functionally highly active, especially when exposed to cold. Although combined positron emission tomography (PET) and computed tomography (CT) is an expensive method, it has provided new and important data on the role of BAT in human physiology and metabolism. Currently, PET seems to be the only option for the study of BAT function and its interaction with other tissues at the whole-body level. Further studies are needed to evaluate the importance of BAT in human physiology, and to evaluate the possible manipulation of BAT activation.

Keywords: Brown adipose tissue, brown fat, human, imaging, positron emission tomography

Human brown adipose tissue (BAT) has recently been re-discovered as a tissue of interest, and it has been found to be functionally and metabolically highly active when exposed to cold [1,2]. Advanced imaging technology – namely the development of hybrid positron emission tomography (PET)/computed tomography (CT) scanners – has been the key to the progress that has been made.

Metabolic activity during oncological diagnostic [18F]2-fluoro-D-glucose (FDG)-PET scanning has been recognized in the upper chest and neck region for a long time; in the 1990s this activity was considered to represent muscle tension in the neck area. The launch of hybrid PET/CT scanners in the 2000s enabled the precise co-localization of PET images with anatomical CT images in non cerebral regions also. When symmetrical uptake of FDG in the neck and upper chest region during PET/CT scanning was carefully analyzed, the metabolic activity was clearly localized in adipose tissue [3]. However, similar accumulation of FDG may occur in the case of inflammation, which cannot be excluded in severely sick cancer patients – especially since the fat area in the supraclavicular region consists of several other structures (such as blood vessels and lymphatic tissue). Thus it was essential to find an answer to the questions whether healthy adults have functionally active BAT in regions of high uptake of FDG, and whether this activated tissue expresses biochemical characteristics typical of BAT.

Increased uptake of FDG in the supraclavicular region has been described more often in cold seasons than during the summer [4]. Saito et al [5] demonstrated a similar kind of accumulation in the neck, supraclavicular, and paravertebral regions in experimental settings in which the study individuals were exposed to acute cold before and during PET/CT scanning. We followed a similar protocol whereby healthy adults were exposed to temperatures of 15–19°C for 2 hours, before undergoing a PET/CT scan during which one foot was intermittently placed into cold water (5–10°C). In addition to detecting any increase in FDG uptake during the cold exposure, we quantified glucose uptake in the suspected BAT regions (in most cases supraclavicular), in order to compare tissue uptake of glucose in the different cold and warm settings. The method of quantification of glucose uptake in human adipose tissue used in our laboratory has been validated previously [6]. Glucose uptake was found to be more than 10 times greater under conditions of cold than that in the scan performed at normal room temperature [1].
The probability of observing increased uptake of FDG in the neck region ranges from 0.6% to 25% [3,4,7–9], the highest probabilities being found during the cold season in females [4]. In our small study population of 27 normal-weight adults, FDG uptake was activated in 60% of cases during experimental exposure to cold.

Although cold is a very effective activator of BAT metabolism and thermogenesis, humans do not spend much time in cold environments. A related alternative condition of everyday life that merits consideration is the postprandial state, in which many of us spend most of our waking hours. Eating is considered to be the trigger for “true” thermogenesis, although the importance of diet-induced thermogenesis in humans has been debated [10]. Furthermore, available data concerning BAT metabolism in postprandial humans are very sparse. Williams and Kolodny [11] have shown that, although uptake of FDG is high in BAT during fasting, this could be abolished by giving two high-fat, very-low-carbohydrate, protein-permitted meals twice, before the scan and during the previous evening. This suggests that the function of the Randle cycle in BAT is similar to that in other tissues, such as skeletal muscle.

The important question is whether the postprandial thermogenic effect is local or systemic. Regarding the small amount of BAT in healthy normal-weight adults – 1–60 g in the supraclavicular region – we would support the concept of a local release of heat, in view of our own experience from cold exposure studies in which we have not found any change in the skin temperature. Therefore, in the postprandial state, activation of thermogenesis in the supraclavicular and neck regions would secure the delivery of warm blood to the brain during the period when the peripheral circulation was concentrated mostly in the gastrointestinal tract.

One of the hormones secreted simultaneously with eating is insulin, from the pancreatic β cells. Our preliminary data suggest that insulin may have a considerable role in human BAT metabolism [12]. Uptake of glucose by this tissue is measured by FDG-PET, and insulin stimulation is induced using the euglycemic hyperinsulinemic clamp technique (1 mU/kg per min) [13], whereby the plasma insulin concentration is increased to the postprandial insulin concentration. The insulin-stimulated rate of uptake of glucose is comparable to that which has been measured in skeletal muscle [12]. In the future, it will be intriguing to learn what other factors, such as gut hormones, participate in the function of BAT in human physiology.

PET has become a more common technique in the Western world, but remains very expensive. The need for tracers other than FDG is obvious: it is the tracer most commonly used worldwide (90% of PET scans are performed using FDG), and is currently the only tracer used in the study of human BAT function; this may lead to bias. Even when fully activated, BAT derives only about 10% of its energy source from glucose [14]. For the study of BAT function in human metabolism, it would be highly desirable to utilize new tracers that could increase our understanding, for example, of adrenergic receptor density or fatty acid metabolism in BAT. However, other modalities for the imaging of BAT function remain to be developed. To date, magnetic resonance imaging (MRI) has not been able to fulfill the criteria for sensitivity, and for the present MRI is comparable to CT in imaging anatomy, but is not able to distinguish between white and brown fat in humans (Figure 1). Functional MRI could...
be an option for the future, although with the same provisos as for PET: the imaging conditions (warm/cold/fasting/postprandial) need to be taken carefully into account before conclusions are draw. We found this to be crucial when an increase in uptake of FDG in BAT during exposure to cold was observed in 60% of study individuals, but none showed any activation of BAT glucose uptake in warm temperatures (Figure 2) [1].

Conclusion

PET is a highly sensitive, non invasive tool for the in vivo imaging of BAT in humans, providing unique information on the basic function and physiology of BAT. Currently, PET seems to be only option for the study of BAT function and its interaction with other tissues at the whole-body level.

REFERENCES

Stimulating brown fat: a potential future therapeutic approach for obesity and insulin resistance?

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Conflicts of interest: None.

Abstract

The failure of current strategies aimed at the containment and treatment of the obesity epidemic has prompted the search for novel targets for therapeutic intervention. The recent discovery that brown adipose tissue (BAT) activity can be detected in a substantial proportion of the adult population has generated a renewed interest in the study of this tissue. As the physiologic activation of BAT can rapidly increase intracellular tri-iodothyronine (T3), generating a local, tissue-specific “thyrotoxicosis” and a substantial increase in energy dissipation in the form of heat, this tissue can be considered a potential therapeutic target for the development of treatments for obesity.

Heart Metab. 2010;48:19–22.

Keywords: Adaptive thermogenesis, brown adipose tissue, deiodinase, insulin resistance, obesity, therapy

The obesity epidemic, with its prohibitive health care and societal costs [1], and the poor success record of available interventions, either behavioral or pharmacological, have prompted the search for novel therapeutic targets and modalities. The past two decades have seen a major push towards obesity research, as demonstrated by an almost 10-fold increase in scientific output in this area over the past 20 years: a simple PubMed search for the topics “obesity” and “therapy” produced 673 results for the year 1989, 1601 for the year 1999, and 5758 for the year 2009.

Besides reducing energy intake through dietary, pharmacological, or surgical means, interventions aimed at increasing energy expenditure would appear to provide a logical method of producing a sustained negative overall energy balance, ultimately resulting in weight loss. Even a small but sustained increase in the resting energy expenditure, which represents approximately 65–85% of total energy expenditure in individuals not engaging in high-intensity manual work, would produce a significant dispersion of calories over time, and, in the absence of significant counter-regulatory mechanisms, clinically relevant weight loss. Several pharmacologic approaches have been explored [2–7]; adrenergic stimulants and high doses of thyroid hormone generate a significant increase in resting energy expenditure, but unwanted side effects relating to the neurologic, cardiovascular, and skeletal systems (in the case of thyroid hormone) preclude their clinical use. In contrast, thyrotoxicosis is a model of increased resting energy expenditure, and the use of selective thyroid hormone receptor subtype or target tissue agonists, which retain the ability to increase overall energy expenditure without...
causing organ-specific toxicity, have been considered as targets for drug development [8].

Brown adipose tissue (BAT), by virtue of a high endogenous expression and activity of intracellular type-2 5'-deiodinase (D2), has the unique ability to increase substantially the intracellular concentrations of tri-iodothyronine (T3), the active form of thyroid hormone, without affecting its circulating concentrations [9]. The resulting high intracellular concentrations of T3 positively regulate the transcription of uncoupling protein-1 (UCP-1), which causes the mitochondrial membrane to become “leaky” to protons, rendering the respiration process inefficient [10]. In other words, BAT has the ability to generate a local, tissue-specific thyrotoxicosis, which in turn leads to a net increase in “inefficient” substrate utilization, with consequent energy dispersion in the form of heat aimed at ensuring the maintenance of core temperature in small rodents and in human newborns. This mechanism is positively regulated by the sympathetic nervous system via the norepinephrine-mediated activation of BAT β3-adrenergic receptors [11], whereas substrate-dependent proteasome-mediated degradation of D2 allows rapid switch-off of this enzymatic reaction [12]. The ability to inactivate this D2-mediated process rapidly is particularly important evolutionarily, as BAT activation comes at an exorbitant cost, from an energy conservation standpoint, when energy (food) availability is the limiting factor for survival and propagation of the species. A notable exception to this rule is represented by “homo technologicus”, which has at its disposal virtually unlimited access to food, without the need to expend significant amounts of energy in order to gather food, evade or defend himself from predators, or maintain core body temperature.

An increase in sympathetic nervous system tone mediated by exposure to cold is not the exclusive pathway of BAT activation. The thermic effect of food – that is, the increase in energy expenditure associated with food intake not explained by the digestion and absorption of nutrients [13], has been attributed to BAT [14]. Recently, Watanabe and co-workers [15] have mechanistically demonstrated that, in mice, bile acids’ act as endocrine signalers for the activation of D2 in BAT via interaction with the transmembrane G-protein coupled receptor, TGR5, and that administration of pharmacologic doses of bile acids positively regulates the transcription of UCP-1, thus generating a local, tissue-specific thyrotoxicosis, which in turn leads to a net increase in “inefficient” substrate utilization, with consequent energy dispersion in the form of heat aimed at ensuring the maintenance of core temperature in small rodents and in human newborns. This mechanism is positively regulated by the sympathetic nervous system via the norepinephrine-mediated activation of BAT β3-adrenergic receptors [11], whereas substrate-dependent proteasome-mediated degradation of D2 allows rapid switch-off of this enzymatic reaction [12]. The ability to inactivate this D2-mediated process rapidly is particularly important evolutionarily, as BAT activation comes at an exorbitant cost, from an energy conservation standpoint, when energy (food) availability is the limiting factor for survival and propagation of the species. A notable exception to this rule is represented by “homo technologicus”, which has at its disposal virtually unlimited access to food, without the need to expend significant amounts of energy in order to gather food, evade or defend himself from predators, or maintain core body temperature.

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The potential role of human BAT in the pathophysiology of obesity, or as a target for therapeutic intervention, has been considered for several decades [16], but this line of research has not been fully pursued, as human intrascapular BAT disappears during the early postnatal period, and the few nests of multiloculated adipocytes resembling BAT that persist have been considered too small to have a significant impact on metabolism. Until recently, the occasional finding of diffuse BAT in individuals chronically exposed to cold [17] or in patients affected by pheochromocytoma [18], and of occasional bilateral tracer uptake in the neck region of patients undergoing positron emission tomography (PET) scans [19], especially during the winter months, have been considered incidental findings devoid of clinical relevance.

Very recently, a series of manuscripts have clearly demonstrated that active BAT can be detected by PET in a substantial proportion of the population [20,21], that, in humans (similarly to rodents), BAT is activated by exposure to cold [22,23], and that the presence of active BAT demonstrated by PET is inversely associated with obesity and traits of the metabolic syndrome [20]. A recent case report further illustrated the potential metabolic role of BAT in humans: the reversal of poorly controlled diabetes in a patient affected by a severe form of insulin resistance (secondary to a mutation in the alpha subunit of the insulin receptor) was linked to the presence of diffuse deposits of BAT, possibly stimulated by supraphysiologic doses of thyroid hormone required for treatment of thyroid cancer. Interestingly, when levothyroxine treatment was suspended for a diagnostic iodine-131 scan, glycemic control deteriorated acutely, concomitant with a loss of BAT activity on PET scan [24]. The clinical data from this very unusual case illustrate the ability of BAT to generate insulin-independent glucose disposal. Taken together, these findings have contributed to a renewed interest in this tissue as a target for the development of pharmacologic intervention for the treatment of obesity, insulin resistance, and their complications [25].

In contrast, the increased amount of subcutaneous fat present in obese individuals may provide natural insulation, dampening thermal dispersion, thus making obese individuals more “energy efficient”; in this case the threshold for activation of BAT would seldom be reached. If this is true, it would represent yet another obstacle on the path toward weight loss. Moreover, current human studies have not yet proven that BAT per se has physiologic relevance in humans, and indeed this finding could be simple association rather than proof of causation. Nonetheless, it is important to note that, in humans, a diffuse “BAT-like” activity can be ascribed to skeletal muscle; such activity in skeletal muscle, well below the level of detection by PET, could play a significant metabolic role. In this regard, targeting whole-body adaptive thermogenesis, irrespective of the anatomical or tissue distribution, could be a viable intervention.
New therapeutic approaches

Brown fat stimulation as a therapeutic approach

Table 1. Potential molecular targets and strategies aimed at activation of brown adipose tissue.

<table>
<thead>
<tr>
<th>Target</th>
<th>Intervention</th>
<th>Potential untoward effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sympathetic nervous system</td>
<td>Central stimulation, catecholamine analogs</td>
<td>Generalized effects of sympathetic overactivity (e.g., cardiac toxicity, hypertension, anxiety)</td>
</tr>
<tr>
<td>β&lt;sub&gt;1&lt;/sub&gt;-Adrenergic receptor</td>
<td>Cold exposure</td>
<td>Counter-regulatory mechanisms, poor tolerability</td>
</tr>
<tr>
<td>G-proteins, cAMP</td>
<td>Selective agonist</td>
<td>Non specific effects on other adrenergic receptor subtypes</td>
</tr>
<tr>
<td>TGR5</td>
<td>Increase intracellular concentrations of cAMP</td>
<td>Generalized effects, cell proliferation</td>
</tr>
<tr>
<td>Type-2 5'-deiodinase</td>
<td>Bile acids analogs</td>
<td>Systemic effects of increased intracellular T3 concentrations (central nervous system, hypothalamic–pituitary–thyroid axis)</td>
</tr>
<tr>
<td>Thyroid hormone receptor</td>
<td>Tissue-selective agonist</td>
<td>Spill-over systemic thyrotoxic effects</td>
</tr>
</tbody>
</table>

T3, tri-iodothyronine; TGR5, transmembrane G-protein-coupled receptor 5.

Figure 1. Schematic diagram of brown adipose tissue activation, showing potential therapeutic targets. AC, adenylate cyclase; β<sub>1</sub>, β<sub>1</sub> adrenergic receptor; CRE, cAMP-responsive element; D2, type-2 5'-deiodinase; RXR, retinoid X receptor; T3, tri-iodothyronine; T4, thyroxine; TRE, thyroid-hormone-responsive element; TGR5, transmembrane G-protein-coupled receptor 5; UCP-1, uncoupling protein-1.

Table 1 and Figure 1 illustrate potential molecular targets and strategies aimed at the activation of BAT.

Conclusion

The demonstration that BAT is present and active in adult humans has renewed interest in the physiology of this tissue and its potential as a target for pharmacologic intervention. Conversely, a word of caution comes from the consideration that a chronic activation of BAT may generate a state of high-energy flux, and that compensatory mechanisms would probably ensue, mitigating the potentially beneficial effects on substrate metabolism and on the overall energy balance.

1. see glossary for definition of these terms.

REFERENCES


Clinical benefits of trimetazidine in diabetic patients with coronary artery disease

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Abstract
The worldwide prevalence of diabetes mellitus, and in particular type 2 or non insulin-dependent diabetes mellitus, which accounts for up to 90% of the diabetic population, is currently increasing. Diabetes mellitus is an independent risk factor for coronary artery disease, the incidence of which in diabetic populations is about 55%. Conventional treatment strategies for diabetic patients with coronary artery disease include pharmacological treatments such as β-blockers, calcium channel blockers, and nitrates, and revascularization therapy such as percutaneous coronary interventions and coronary artery bypass graft surgery. The metabolic approach is an innovative therapeutic strategy for these patients. Trimetazidine, the first of a new class of metabolic agents, the 3-ketoacyl coenzyme A thiolase (3-KAT) inhibitors, is an effective antianginal agent that shifts cardiac energy metabolism from fatty acid oxidation to glucose oxidation by inhibiting long-chain 3-KAT. In different studies, trimetazidine has shown a significant anti-ischemic effect on myocardial ischemia in diabetic patients with stable angina, in addition to producing an improvement in exercise tolerance. It also has favorable effects in patients with diabetes who have silent ischemia. Furthermore, treatment with trimetazidine has led to improvements in left ventricular systolic and diastolic functions, in addition to its protective effect on the vascular endothelium in patients with diabetic ischemic cardiomyopathy. Because of its effect on cardiac metabolism at rest, and its effects on myocardial ischemia and left ventricular function, trimetazidine should always be considered for the treatment of diabetic patients with ischemic heart disease with or without left ventricular dysfunction.

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Keywords: Coronary artery disease, diabetes, metabolism, trimetazidine

Introduction
The prevalence of coronary heart disease increases from 2–4% in the general population to as much as 55% among adult patients with diabetes [1]. Diabetes mellitus is an important risk factor for future cardiovascular events in patients with ischemic heart disease, as well as in patients without heart disease [2,3]. Diabetic patients without overt coronary artery disease have a prognosis similar to that of non diabetic patients with coronary disease, whereas diabetic patients with coronary disease have a cardiovascular death rate double that of those without diabetes [4]. In addition, patients with diabetes and coronary heart disease have an increased incidence of heart failure. This is the result of accelerated atherogenesis, with involvement of peripheral coronary segments and altered myocardial metabolism, both of which lead to diffuse hibernation. The different and more diffuse distribution of atherosclerosis in patients with type 2 (non insulin-dependent) diabetes mellitus compared with that in the general population of patients with
coronary artery disease is related, at least in part, to the metabolic derangements of diabetes and to the clustering of different risk factors such as increased blood pressure, central obesity, and altered lipid profile [5]. The clinical presentation, the pathophysiology of myocardial ischemia, and the progression of both atherosclerosis and heart failure in patients with diabetes mellitus are different from those without diabetes. Although angina is the most common presentation of patients with coronary artery disease, patients with type 2 diabetes mellitus have a lower incidence of anginal pains and a higher incidence of silent myocardial ischemia or myocardial infarction than those without diabetes [6,7], and about 30% of diabetic coronary artery disease patients show evidence of silent ischemia, either during daily activity or during provocative tests.

Cardiac metabolism in diabetic patients with coronary artery disease

Under normal conditions, the heart is capable of oxidizing different substrates, such as carbohydrates or free fatty acids (FFA), to produce energy. The ability of the heart to switch from one substrate to the other is fundamental to its health, enabling it to adapt to many different factors, such as substrate availability, tissue perfusion, hormonal regulation, and the amount of cardiac work [8]. The normal heart obtains 60–90% of its energy from FFA oxidation and the remainder from glucose and lactate. Although FFA metabolism produces more ATP per gram of substrate, it has a greater requirement for oxygen because it is less efficient.

In type 2 (non insulin-dependent) diabetes mellitus, myocardial glucose transport, glycolysis, and glucose oxidation are all decreased, and a switch to fatty acid oxidation can provide 90–100% of the ATP requirements of the heart. Decreased glucose uptake resulting from insulin deficiency can partly explain the decrease in glucose metabolism, but high concentrations of circulating fatty acids and alterations in the control of fatty acid oxidation appear to be primarily responsible for this switch [9]. However, the fatty acid oxidation is less effective with respect to energy production because it produces less ATP per mole of oxygen used, and therefore more oxygen is required for ATP production when hearts are metabolizing fatty acids than when they utilize glucose. In addition, fatty acids can induce uncoupling of mitochondria, perhaps by upregulation of the expression and activity of uncoupling proteins [8,10]. Finally, the low rate of glucose oxidation results in increased proton production in the heart because of an uncoupling of glycolysis from glucose oxidation [9]. All these factors, together with the accumulation of glucose and fatty acid metabolic intermediates in the cells, contribute to a deterioration in myocardial cell function [8,10]. This decreases the efficiency of the heart muscle, resulting in decrease in cardiac work per molecule of oxygen consumed. Decreased cardiac efficiency exacerbates the imbalance between oxygen supply and demand that occurs during ischemia [9].

Rationale for the use of anti-ischemic metabolic agents in patients with type 2 diabetes mellitus

The classic treatment of angina involves drugs that affect cardiovascular hemodynamics (β-blockers, calcium channel blockers, and nitrates), thereby reducing myocardial energy demand. Many of these patients with type 2 diabetes are also undergoing myocardial revascularization, with either percutaneous coronary interventions or coronary artery bypass graft surgery. However, these treatment modalities are sometimes incapable of controlling anginal symptoms and halting the disease process, which leads to progressive contractile dysfunction and left ventricular enlargement. Moreover conventional anti-ischemic agents have systemic hemodynamic effects that reduce patient compliance. In the case of myocardial ischemia, the increase in fatty acid oxidation inhibits the enzyme pyruvate dehydrogenase – an effect that suppresses glucose oxidation. The result of this inhibiting effect is an increase in lactate production and a decrease in intracellular pH in the ischemic cell; this, in turn, leads to impaired myocardial contractile function, as the production of ATP that is required to restore intracellular homeostasis is reduced. The accumulation of fatty acid intermediates during β-oxidation has been shown to induce diastolic left ventricular dysfunction and to lower the threshold for the development of ventricular arrhythmias during myocardial ischemia [11]. Ischemia is always associated with metabolic disturbances that should be addressed specifically, alongside all other factors that contribute to the development of angina. Metabolic consequences of myocardial ischemia are serious, in both the short and the long term, and therefore early and effective treatment is required for this metabolic problem.

Trimetazidine, the metabolic modulator

The modulation of fatty acid metabolism can be obtained by drugs that inhibits their oxidation. Trimetazidine (Vastarel MR), the first of a new class of metabolic agents, the 3-ketoacyl coenzyme A thiolase (3-KAT) inhibitors [12,13], is an effective antianginal agent that shifts cardiac energy metabolism from fatty
heart metabolism

Acid oxidation to glucose oxidation by inhibiting mitochondrial long-chain 3-KAT [13]. The benefits of increased glycolytic substrate utilization are attributed to several mechanisms. The expected number of moles of ATP produced per mole of oxygen consumed is 12% greater for glucose oxidation than for FFA oxidation, although it is reasonable to believe that improvement in glucose metabolism may increase ATP production by up to 30% [5]. By decreasing fatty acid oxidation, trimetazidine stimulates glucose utilization, restoring coupling between glycolysis and carbohydrate oxidation, and leading to the production of ATP with less oxygen consumption [12]. In addition, trimetazidine stimulates the turnover of membrane phospholipids during ischemia and reperfusion, redirecting fatty acids towards phospholipids, and increasing cell tolerance to ischemia-reperfusion damage. The anti-ischemic properties of trimetazidine are independent of hemodynamic changes, and are associated with a greater recovery of mechanical function after ischemia [5]. Metabolic modulators such as trimetazidine are effective in the treatment of myocardial ischemia, whether silent or symptomatic, and in improving left ventricular systolic and diastolic functions in patients with diabetes and coronary artery disease.

Trimetazidine in patients with diabetes, chronic stable angina, and silent ischemia

The TRIMetazidine in POLand 1 (TRIMPOL-1) study showed that treatment with trimetazidine for 4 weeks in diabetic patients with chronic stable angina significantly reduced the number of anginal episodes and improved myocardial ischemia and exercise capacity [14]. Rosano and colleagues [15] showed that, in this patient population, the addition of trimetazidine to standard medical treatment reduced the number of episodes of ST-segment depression, the number of episodes of silent ischemia, and the total duration of silent myocardial ischemia over 24 h, and reduced the total ischemic burden. Marazzi and coworkers [16] evaluated the metabolic effect of trimetazidine in patients with diabetes and coronary artery disease. They found that trimetazidine significantly decreased the incidence of silent and symptomatic episodes of myocardial ischemia (by 24%), and the number of episodes and total duration of silent myocardial ischemia over 24 h (by 42% and 37%, respectively) (Figure 1).

In the DIETRIC study, which included 580 patients, Rodriguez Padial and colleagues studied the efficacy and tolerability of trimetazidine, combined with regular medical treatment, in diabetic coronary artery disease patients. Trimetazidine reduced the incidence of anginal episodes, improved results in the exercise tolerance test, and increased the time to ST-segment depression [17].

Trimetazidine in diabetic patients with ischemic cardiomyopathy

Partial inhibition of fatty acid oxidation may represent an alternative approach to the treatment of diabetic patients with heart failure. As a result of the preferential promotion of glucose and pyruvate oxidation, trimetazidine improves the activities of the sodium-potassium ATPase and calcium uptake pumps of the sarcoplasmic reticulum that are, respectively, responsible for left ventricular systolic depolarization and diastolic relaxation. In addition, the metabolic effects of trimetazidine translate into a reduced total ischemic burden and a better utilization of metabolic substrates, which translate into greater mechanical efficiency [18–23].

Fragasso and colleagues studied the short- and long-term beneficial effects of trimetazidine in patients with diabetes and ischemic cardiomyopathy, and found that the drug improved left ventricular function, symptoms, glucose metabolism, and endothelial function [24]. Another group of investigators studied the effect of trimetazidine on myocardial perfusion and left ventricular systolic function in diabetic patients with ischemic cardiomyopathy and reported that it improved left ventricular systolic function (by 16%) (Figure 2) and functional capacity, despite no change in myocardial perfusion [25]. Rosano et al [15] reported that the addition of trimetazidine to standard treatment caused a significant reduction in left ventricular systolic and diastolic diameters, a significant decrease in left ventricular diastolic–systolic volume index, an improvement in left ventricular systolic and diastolic functions, and a significant decrease in the wall motion score index of chronically dysfunctional...
myocardium in patients with type 2 diabetes mellitus, coronary artery disease, and reduced left ventricular function [15]. Monti and colleagues [26] demonstrated that trimetazidine has positive effects on the peripheral vasculature and skeletal muscle metabolism in diabetic patients with ischemic cardiomyopathy. Treatment with trimetazidine for 15 days increased glucose utilization in skeletal muscle, and reduced the release of endothelin-1 compared with placebo, suggesting a protective effect on the vascular endothelium.

Summary

Trimetazidine is the first of an innovative class of metabolic agents. It has been shown that it has beneficial effects in patients with type 2 diabetes mellitus and stable coronary artery disease, improving ischemic episodes whether silent or symptomatic. It also has a favorable effect in improving both left ventricular systolic and diastolic functions in patients with diabetic ischemic cardiomyopathy.

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Comorbidity in the obese patient: the paroxysmal Pickwickian with pulmonary peculiarities and poor pump performance

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Conflicts of interest: None.

Abstract
Obesity is a growing epidemic worldwide and presents an important challenge to health care providers as a result of its association with chronic health conditions and early mortality. Treatments aim to target obesity itself, and the comorbid complications that may arise from it. Early diagnosis and treatment are paramount. However, symptoms are often multifactorial in etiology, and can be difficult to dissociate from one another. Furthermore, diagnostic tests and interventions can also be particularly challenging in this patient population.


Keywords: Airways disease, atrial fibrillation, breathlessness, comorbidities, heart failure, obesity

Introduction
The growing level of obesity in developed countries is expected to fuel a surge in cardiovascular diseases over the next few decades, with significant increases in arterial hypertension, coronary artery disease, heart failure, and stroke (Table I) [1]. Early disease detection and prompt intervention are of particular importance in this high-risk group. However, accurate symptom assessment can be challenging at times, driven by the presence of several, and potentially contributory, comorbidities, in addition to the recognized practical limitations in available diagnostic tests. We present a case report of a patient with obesity under multidisciplinary care for symptoms of breathlessness, in whom many of these issues arise.

Case report
A 58-year-old lady was referred for further assessment of exertional breathlessness by her endocrinologist in January 2008. Her medical history at this time was remarkable for morbid obesity (body mass index [BMI] 41.1 kg/m² and waist circumference 110 cm), cerebrovascular disease, hypothyroidism, tablet-controlled diabetes mellitus, and previous venous thromboembolism, for which she was receiving lifelong anticoagulation agents. The patient was a lifelong smoker. She also complained of morning headaches, peripheral edema, and daytime somnolence (Epworth sleepiness score 19).

Initial investigations revealed a resting arterial oxygen pressure of 7.5 kPa, with compensated hypercapnia (pCO₂ 8.1 kPa, HCO₃⁻ 32 mmol/L, pH 7.36).
A high apnea–hypopnea index on overnight oximetry suggested superimposed obstructive sleep apnea. There was marked restriction on pulmonary function testing (forced vital capacity [FVC] 1.36 L) consistent with her obesity, but also obstruction to flow (forced expired volume in 1 s [FEV 1] 0.8 L, FEV 1/FVC = 0.59) with moderate reversibility on salbutamol challenge. Pulmonary embolism was excluded by computed tomography pulmonary angiography. The patient was hypertensive, with a deranged lipid profile. Echocardiography was limited by poor windows related to body habitus. Transthoracic imaging with intravenous contrast suggested preserved biventricular systolic function, diastolic impairment (E/E′ 15), bi-atrial dilatation, and increased pulmonary artery pressures (mean 58 mm Hg).

Loop diuretics and an angiotensin-converting enzyme (ACE) inhibitor were commenced in addition to her regular medications. The patient was established on domiciliary continuous positive airways pressure (CPAP) with supplemental oxygen. These interventions helped considerably with her fatigue, peripheral fluid retention, and blood pressure control. Her BMI reduced modestly to 38.9 kg/m 2 in combination with targeted anti-obesity medication under close outpatient surveillance by the endocrinologists. However, she required admission to hospital on several occasions throughout 2008 for infective exacerbations of her airways disease and fluid retention. Furthermore, she remained very limited by persistent exertional dyspnea.

Towards the end of 2008, it became apparent that the patient was experiencing paroxysms of atrial fibrillation with rapid ventricular conduction, which was considered contributory to her continuing symptoms (Figure 1). She was reluctantly commenced on amiodarone therapy, given her background airways fragility and underlying thyroid dysfunction. Coincidentally, she developed left bundle bunch block (QRS duration 142 ms) at this time and described intermittent chest pains unrelated to her arrhythmia. Repeat contrast echocardiography demonstrated delayed septal contraction, consistent with her conduction disease, and a marked deterioration in her cardiac function, with a calculated ejection fraction now of 30%. This was confirmed on a myocardial perfusion scan, together with probable anterolateral ischemia on dobutamine stress testing, although again there was considerable signal attenuation and artefact as a result of body habitus. Her weight and pulmonary congestion made it very difficult for her to lie flat, but coronary angiography performed with CPAP support and light sedation via the radial approach reassuringly demonstrated normal anatomy.

By autumn of 2009, the patient’s BMI was static at 38 kg/m 2, but she was not considered fit for bariatric surgery. She had required several admissions for optimization of her ventilatory support earlier in the year. CPAP therapy was converted to non invasive ventilation because of poorly controlled hypercapnia (Figure 2) and she was commenced on home nebulizers. Her arrhythmia burden was increasing in frequency and severity, with very poor rate control during atrial fibrillation despite the addition of high-dose digoxin and a calcium channel antagonist. Her ejection fraction (in sinus rhythm) remained impaired on optimal ACE inhibition and the addition of a potassium-sparing agent to her diuretic regimen. Her medical care at this stage was coordinated predominantly between respiratory, cardiology, and endocrine services, with cross-disciplinary support throughout from physiotherapy, occupational therapy, and social services. There was additional input from psychiatry and palliative care because of her deteriorating quality of life.

### Table I. Predicted percentage increases in obesity-related diseases in England up to the year 2050. (From Brown et al [1]; National Heart Forum report on data collected by the Health Survey for England (1993–2007), with permission.)

<table>
<thead>
<tr>
<th>Disease</th>
<th>Predicted percentage increase in disease rates by year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2010</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Stroke</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2</td>
</tr>
<tr>
<td>Arthritis</td>
<td>1</td>
</tr>
<tr>
<td>Gall bladder disease</td>
<td>0</td>
</tr>
<tr>
<td>Breast</td>
<td>2</td>
</tr>
<tr>
<td>Colorectal</td>
<td>3</td>
</tr>
<tr>
<td>Endometrial</td>
<td>1</td>
</tr>
<tr>
<td>Esophageal</td>
<td>8</td>
</tr>
<tr>
<td>Kidney</td>
<td>7</td>
</tr>
<tr>
<td>Liver</td>
<td>0</td>
</tr>
</tbody>
</table>

Heart Metab. 2010; 48:28–31
In early 2010, the patient’s condition had degenerated to sustained atrial fibrillation and she was really quite limited in simple activities. She was not considered fit for general anesthetic for external cardioversion, and therefore underwent internal cardioversion under local anesthetic and sedation, with a reasonable improvement in her breathing. Her arrhythmia is anticipated to return, however, and her systolic ventricular function remains markedly depressed. She is being considered for permanent pacing (with an additional left ventricular lead for cardiac resynchronization) and atroventricular node ablation as a safer alternative to pulmonary vein intervention for control of the atrial fibrillation and heart failure.

**Comorbid disease in the obese patient**

The prevalence of comorbid disease is significantly increased in overweight and obese individuals [2]. In some cases, it is difficult conclusively to dissociate cause from effect. However, as active weight loss reduces this increased risk to health, it is likely that...
Case report
Comorbidity in the obese patient

obesity contributes directly towards the pathogenesis in many of these disease processes [3–7]. This case report demonstrates some of the complexities in the management of comorbid conditions in the obese patient, and also highlights the importance of a multidisciplinary approach to health care provision in this population. With increasing levels of obesity worldwide, this is, unfortunately, set to become an all too familiar scenario for clinicians.

REFERENCES


Mitochondrial uncoupling proteins

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Conflicts of interest: None.

Abstract
The aim of this review is to provide an overview of current knowledge on the three mammalian uncoupling proteins, UCP-1, UCP-2, and UCP-3.

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Keywords: Diabetes, energy expenditure, immunity, obesity, reactive oxygen species, thermogenesis, uncoupling proteins

Thermogenic uncoupling protein in brown adipose tissue
The concept of mitochondrial uncoupling protein comes from the thermogenic organ of mammals known as brown adipose tissue [1]. This is a specialized type of fat tissue in which the cells (brown adipocytes) contain many more mitochondria, and less lipid, than normal fat (white adipocytes). These mitochondria contain a specialized protein, uncoupling protein (UCP-1). When introduced into artificial membranes, UCP-1 increases the permeability of the membrane to protons [2]. According to the chemiosmotic theory of Mitchell, oxidization of substrate by mitochondrial respiratory chain causes proton pumping and thus creates an electrical and pH gradient across the mitochondrial inner membrane, which is the intermediate that creates a tight link (coupling) between substrate oxidation and production of the energy-rich molecule, ATP. The proton conductance created by UCP-1 dissipates this potential, whereas the oxidation of substrates attempts to maintain it [3]. This greatly accelerates metabolism, and results in an intense production of heat. This raised interest, because the consequence of the activity of brown adipose tissue on energy expenditure is the same as that of exercise (Figure 1). However, in humans, active brown adipose tissue was recognized only in newborns. Recently, the use of positron emission tomography has revealed a significant percentage of young adults with active brown fat – which, furthermore, reacts to external temperature [4].

The emergence of “new” uncoupling proteins
Uncoupling protein-1 appeared to be a mammalian acquisition linked to regulation of body temperature. When the protein sequences were made available, it became apparent that it and other transporters in the mitochondrial inner membrane share common properties [5]; there is a shared motif of amino acids, which provides a useful criterion for the recognition of a “mitochondrial carrier” of this nature; six transmembranous alpha helices are usually present; the sequence length is usually approximately 300 amino acids. The 3-dimensional structure of one member of this family of transporters, the ADP/ATP translocator, has been determined [6].

In the late 1990s, several sequences very similar to that of UCP-1 were discovered [7]. Two were described in mammals (UCP-2 and UCP-3) and one in birds, but “UCPs” were also found in plants and cold-blooded animals. Consequently, their participation in thermogenesis was questioned. However, it was relatively easily demonstrated that, under certain conditions, they could transport protons, and they were therefore considered to be new uncoupling proteins. There are reports of UCPs-4 and -5 in mammals; however, the similarity of these two proteins to UCP-1 is much lower.

Molecular mechanisms
The uncoupling activity of UCP-1 is tightly regulated: binding of nucleotides inhibits transport by UCP-1,
whereas free fatty acids stimulate proton transport by UCP-1. This has the consequence that mitochondria could be fully “prepared” for thermogenesis, primed with a large supply of UCP-1 that remains fully inhibited by endogenous nucleotides and the absence of fatty acids; when activation occurs, however, thermogenesis starts within seconds [1]. The process of activation involves adrenergic stimulation that triggers lipolysis, which provides fatty acids for mitochondrial oxidation that in turn simultaneously stimulate proton transport by UCP-1 [3]. Moreover, adrenergic stimulation is the last step necessary for a maximal transcription of the Ucp1 gene, which is also activated by nuclear receptors such as peroxisome proliferator activated receptors (PPARs), retinoic acid, and thyroid hormone receptors [8], with the participation of the coactivator, proliferator-activated receptor-gamma coactivator-1 (PGC-1). The transcription of Ucp2 and Ucp3 genes, although not sensitive to adrenergic stimulation, is also under the control of nuclear receptors, in particular PPARs that mediate the transcriptional response to fatty acids [9]. The regulation of mRNA translation plays a significant role in the case of UCP-2 [10].

The mechanism of proton transport by UCPs remains a matter of debate [11]. One proposal is that proton transport is the indirect consequence of the transport of an anionic hydrophobic “activator” (Figure 2a). This mechanism is shared with other proteins not known to be UCPs [12], and the new UCPs could probably act similarly with activators that might be different than those involved with UCP-1. The physiological relevance of this cycle has been questioned, and the alternative proposal put forward that UCP-1 uses a specific proton transport mechanism [5] (Figure 2b). If the latter is the case, it remains to be determined whether or not “new UCPs” possess a similar property. It has also been suggested that only half of the cycle is relevant, and that the new UCPs drive fatty acids out of mitochondria [13,14]. All these mechanisms of transport are much less efficient than that afforded by transport channels: the amount of transporter present is clearly a limiting factor, and a quantitatively significant uncoupling is associated with a high level of expression of UCP-1. In contrast, the new UCPs are much less abundant, which sometimes renders their detection questionable.

**Physiology**

Uncoupling increases energy expenditure and leads to weight loss. Accordingly, the chemical uncoupler, dinitrophenol (now completely banned because of side effects), was, for a period, used to trigger weight loss. Conversely, UCP knockout was expected to decrease energy expenditure, with obesity as a consequence. Although overexpression of UCPs provided resistance against obesity in animal models, knockout of individual UCP genes failed to produce obese...
animals: (1) UCP-1 appeared to be required for cold-induced thermogenesis [15]; (2) no major defect has been associated with the disappearance of UCP-3, which is expressed essentially in muscle [16] (notwithstanding the observation that loss of UCP-3 in mice was associated with disappearance of the metamphetamine induced hyperthermia [17]); (3) inactivation of UCP-2 has led to two observations: a modification of insulin secretion by pancreatic β cells [18] and an increase in immunity [19]. Genipin, a molecule from a plant used in Chinese medicine, appears to be an inhibitor of UCP-2 and could thus be used to improve insulin secretion [20]. There appears to be a consensus of opinion that inactivation of UCP leads to increased oxidative stress. Overexpression of UCPs has produced remarkable examples of protection against ischemic or traumatic shock in which oxidative stress contributes heavily to the damage sustained. Modifications observed in transgenic animals (or cellular models) could be accounted for by variation of mitochondrial activity and eventual “uncoupling”. However, this uncoupling has been difficult to demonstrate. It may be because it is of modest degree, which would be in agreement with the level of expression of UCP-2/3. Alternatively, uncoupling is not the explanation, and the observed phenotypes are to be explained by a different transport activity of UCP-2/3 leading to subtle modification of mitochondrial metabolism, not yet understood at the molecular level [21].

Conclusion and perspectives

To summarize the present situation, the well defined physiological role of UCP-1 contrasts with a more confused situation with regard to the other UCPs discovered 20 years later. It may be considered that there is consensus over the following points in the case of the “new” UCPs: (1) they are not the explanation for the “basal proton leak” observed in all mitochondria, but, in the opinion of several authors, constitute a supplementary inducible proton leak; (2) their level of expression is orders of magnitude lower than that of UCP-1; (3) their relevance appears to be related to metabolism, rather than to energy expenditure; (4) a link exists between UCPs and the production/handling of reactive oxygen species.

Other aspects of mitochondrial uncoupling proteins that are already under study or deserving consideration include: (1) the question whether or not expression of UCP-1 is strictly restricted to brown adipocytes, which remains a matter of controversy; (2) the relationships between UCP-2, cellular division, and cancer; (3) examining whether any interaction with other proteins occurs and has a physiological relevance, or whether it is valid that the UCPs continue to be considered ‘solitary proteins’ operating a transport system in the mitochondrial inner membrane; (4) the mechanisms by which UCPs are degraded.

REFERENCES

The current state of risk prevention for cardiovascular events has emerged from more than 50 years of epidemiological studies. Biomarkers such as body weight, hyperglycemia, hypertension, and increased serum concentrations of low-density lipoprotein cholesterol have helped to assess cardiovascular risk and have been proposed as therapeutic targets. Drug development programs have used a growing array of markers to identify and evaluate novel drugs, establish dose ranges, prioritize research efforts, and establish new treatment guidelines. Nonetheless, our highly promising contemporary treatment regimens have not been consistently shown to improve clinical outcomes.

Type 2 diabetes mellitus is widely accepted to be a condition associated with a high risk for coronary events, and patients with type 2 diabetes mellitus have been identified as targets for aggressive treatment. However, data from recent studies, including the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial [1] and the Veterans' Affairs Diabetes Trial (VADT) [2], led the investigators to conclude that aggressively and rapidly decreasing glycated hemoglobin (HbA\textsubscript{1c}) to less than 7% in type 2 diabetes mellitus does not improve cardiovascular outcomes. On the contrary, a slight, but statistically significant increase in cardiovascular death was observed in the intensive glycemic control arm in the ACCORD study (Table I).

Following these observations, the role of comorbidities including obesity, hypertension, and dyslipidemia – termed the “cardiometabolic syndrome” – has been emphasized in patients with type 2 diabetes mellitus. Lifestyle interventions designed to modify behaviors such as overeating and inactivity have proven to be effective [3] in reducing the prevalence of these comorbidities and cardiovascular events.

Four large randomized trials recently completed have evaluated the impact of intensive risk factor treatment on cardiovascular mortality, major adverse cardiovascular events, and the extent of coronary artery disease in patients with type 2 diabetes mellitus.

The Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) study examined the effects of the approved diabetes medication, nateglinide – a relatively weak, rapidly acting, sulfonylurea-like drug – and the angiotensin receptor blocker, valsartan, on the development of diabetes and cardiovascular disease [4,5]. Neither drug, nor their combination, offered significant protection from the progression of impaired glucose tolerance to diabetes or from the progression of cardiovascular disease.

The Assessment on the Prevention of Progression by Rosiglitazone on Atherosclerosis in Diabetes Patients With Cardiovascular History (APPROACH) study [6], evaluated the potentially glucose-independent effects of rosiglitazone, a thiazolidinedione, on coronary atherosclerosis, as assessed by intravascular ultrasound. The authors concluded that rosiglitazone did not significantly decrease the primary endpoint of progression of coronary atherosclerosis in patients with type 2 diabetes mellitus and coronary atherosclerosis.

The ACCORD blood pressure (ACCORD BP) study [7] investigators evaluated the potential benefits of targeting a systolic blood pressure less than 120 mm Hg, compared with a value less than 140 mm Hg, in patients with type 2 diabetes.

In the ACCORD Lipid study [8], patients were randomly assigned to receive either simvastatin plus fenofibrate or simvastatin alone. The goal of treatment with fenofibrate was to reduce plasma triglyceride concentrations and increase plasma high-density lipoprotein cholesterol concentrations in patients who were already taking a statin to reduce plasma low-density lipoprotein cholesterol.

In summary, therefore, aggressive control of risk factors did not result in a significant improvement in clinical outcomes. So, despite a sound rationale for the global treatment of cardiovascular risk factors, the...
results of these trials fell far below expectations, being largely negative, and raising many disturbing questions. It has been widely validated that the presence of prespecified clinical and biochemical features are good indicators of increased risk for cardiovascular disease. The possibility of easily identifying and monitoring such indicators has therefore been translated into intensified clinical efforts aimed at their suppression, thereby shifting the relationship between risk factors and cardiovascular disease from “indicators” to “causal mechanisms”.

Changes in clinical features are used directly for determining the clinical benefit of a treatment strategy, and as such are named “surrogate endpoints”. However, the clinical endpoint is the characteristic or variable that truly reflects how a patient feels, functions, or survives. Principal factors that may explain the failure of clinical features to translate into clinical outcomes include:

1. The surrogate does not cause the disease. In fact, although many potential surrogates correlate with clinical outcome, very few are able to reflect the full therapeutic effect on the clinical outcome, suggesting the existence of a bridging gap between the two variables. In the APPROACH study, for example, treatment effect was rated as effective or not, depending on the change in plaque volume measured by intravascular ultrasound. However, convincing evidence that links this parameter to benefit with respect to cardiovascular risk is still lacking. Moreover, although atherosclerotic disease often results in flow-limiting lesions, most patients die of an acute coronary syndrome, usually associated with non flow-limiting lesions.

2. The surrogate is involved in only one pathway of a multiple-pathway disease. The study populations being considered in the aforementioned studies were diabetic patients, with accompanying comorbidities such as obesity, hypertension, and dyslipidemia. It is now well accepted that there is a common, as well as complex, network of underlying pathophysiological mechanisms leading to a clinical state of increased risk for cardiovascular events. The results of these trials are a further master stroke for the paradigm of the pathophysiology of type 2 diabetes mellitus or other cardiovascular risk factors regarded as a simple “cause-and-effect” disease.

3. The effect of the intervention may prove to be beneficial irrespective of the “suppression” of a surrogate. This is the case with the clinical benefit from statin therapy, which is called a “pleiotropic” effect (to all intents and purposes, an “unidentified surrogate endpoint”).

**Conclusion**

We are left with an apparent paradox: most of the reduction in cardiovascular mortality and morbidity reported in recent years has been attributed to preventive measures, but these same preventive measures, when individually tested in high-risk subgroups of patients, often fail to improve clinical outcomes. The paradox could be explained either by a beneficial effect of the tested drug that is independent of specific risk factor reduction, or by a predominant effect of non pharmacological interventions commonly given in association with drug prescriptions, such as advice on lifestyle changes, rehabilitation programs, and changes in diet.

**REFERENCES**


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**Table 1. Main findings of the ACCORD study. Outcomes of intensive glycemic control.**

- Increased mortality (prespecified secondary outcome and safety measure: 22% higher rate in the intensively treated group; hazard ratio 1.22, 95% confidence interval [CI] 1.01 to 1.46; *P* = 0.04)
- Did not reduce primary outcome over 3.5 years of follow-up (composite of non fatal myocardial infarction, non fatal stroke, fatal cardiovascular disease: 10% lower rate in the intensively treated group; hazard ratio 0.90, 95% CI 0.78 to 1.04; *P* = 0.16)
- Mortality results consistent over several subgroup analyses
- Authors concluded that harm outweighed the potential benefits of intensive treatment
Abstracts and Commentaries: A new link between obesity and heart disease

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Conflicts of interest: None.

Adipocyte Fatty Acid-Binding Protein Suppresses Cardiomyocyte Contraction. A New Link Between Obesity and Heart Disease

Obesity is a major risk factor in the development of the metabolic syndrome and cardiovascular diseases, and seems to be directly related to heart failure independently of other risk factors. Indeed, a direct relationship between increased body mass index and increased risk for heart failure has been demonstrated. Several potential mechanisms are under discussion to explain this correlation, including hemodynamic changes with cardiac overload and left ventricular remodeling, and lipid accumulation into the myocardium, leading to lipoapoptosis in cardiomyocytes. These mechanisms, however, do not fully explain the development of heart dysfunction in obese individuals. Adipocytes are known to produce and release a wide variety of bioactive molecules into the bloodstream. On the basis of these data, the authors have recently demonstrated that mature human adipocytes release substances that strongly and acutely suppress the contraction of cardiomyocytes by attenuating intracellular Ca\(^{2+}\) concentrations. Their previous findings have revealed a hitherto unknown acute depressant effect of adipocyte-derived factors on cardiac contraction, suggesting a new direct role of adipose tissue in the pathogenesis of myocardium dysfunction.

The authors further characterized cardiodepressant activity by fractionating adipocyte secretory products according to molecular weight and proteomic analysis, identifying adipocyte fatty acid-binding protein 4 (FABP4)\(^*\) as the active agent. FABPs are members of a highly conserved family of cytosolic proteins showing a high affinity for long-chain fatty acids and other hydrophobic ligands. FABP4 is predominantly expressed in adipose tissue, and accounts for approximately 1% of total cytosolic protein in human adipose tissue. Cytoplasmic FABP4 is involved in trafficking intracellular fatty acids and other lipid signals by interaction with functional targets. In experimental animal models, FABP4 deficiency protects against the development of diabetes and atherosclerotic cardiovascular disease in both genetic and dietary forms of obesity. Humans with a functional genetic variant of the FABP4 gene, resulting in reduced adipose tissue expression of FABP4, have lower serum concentrations of triglycerides, and are at significantly reduced risk for type 2 diabetes and coronary artery disease. In a recent cross-sectional study, a correlation was observed between circulating concentrations of FABP4 and metabolic syndrome. Together, these clinical and experimental data support a key role for FABP4 in the development of metabolic and cardiovascular complications in obesity.

Commentary
This study by Lamounier-Zepter et al has identified FABP4 as a cardiodepressant factor. Human adipocytes in a primary cell culture system released high amounts of FABP4 into the extracellular medium. FABP4 at concentrations similar to those released by the adipocytes acutely inhibited cardiomyocyte contraction. This effect was concentration-dependent and reduced intracellular Ca\(^{2+}\)-transient. Recent studies from animal models support a novel role for FABP4 in linking obesity with many features of the metabolic syndrome. Mice lacking FABP4 exhibit a protective phenotype against the development of...
insulin resistance associated with genetic or diet-induced obesity. Consistent with these animal studies, a close positive correlation between circulating concentrations of FABP4 and features of the metabolic syndrome has been revealed in humans. On the basis of observations that FABP4 correlates positively with body mass index and fat percentage, and that the murine preadipocyte cell line, 3T3-L1, releases FABP4 into the extracellular medium, adipose tissue has been suggested as being the main source of circulating FABP4. Present findings that human adipocytes in primary cell culture also release FABP4 into the extracellular medium support the role of adipose tissue in the secretion of FABP4 into circulation. Although several studies have pointed to a role of FABP4 in the development of some features of the metabolic syndrome, the pathophysiological mechanisms of circulating FABP4 in mediating the metabolic and cardiovascular complications of obesity remained undetermined.

These are the first research findings to suggest a direct bioactive role of FABP4 in heart function, independently of its role as a transport protein. Interestingly, expression of FABP4 in epicardial adipose tissue has recently been reported, with increased concentrations in patients with metabolic syndrome [1]. Epicardial fat tissue accumulates around the heart and is directly related to intra-abdominal visceral fat and other features of the metabolic syndrome. There are now compelling data pointing to a role of epicardial fat tissue in modulating heart morphology and function. The absence of a fibrous fascial layer between epicardial fat tissue and underlying myocardium permits a close anatomic relationship between both tissues, thus paving the way for factors released from adipocytes to influence myocardial function directly. Consequently, the FABP4 expression found in epicardial fat tissue supports the hypothesis of a direct paracrine effect exerted by FABP4 on the development of heart dysfunction in patients with obesity and metabolic syndrome. In addition, the increase in circulating FABP4 released from subcutaneous and/or visceral adipose tissue in obese individuals could mediate heart dysfunction in those individuals. FABP4 acutely depressed shortening amplitude as well as intracellular systolic peak Ca²⁺ in a dose-dependent manner in isolated rat cardiomyocytes. The heart-specific FABP isoform (FABP3) revealed a similar cardiodepressant effect. It was possible to identify the N-terminal amino acids 1–20 of FABP4 as the most effective cardiodepressant domain. In the absence of any effect of FABP4 on action potential duration and L-type Ca²⁺ current, a reduced excitation–contraction gain caused by FABP4 appears to be the most probable inhibitory mechanism. Both FABP4 and FABP3 are effective in the extracellular medium, thus suggesting a surface receptor for heart and adipocyte FABP. Furthermore, the heart FABP isoform selectively binds to a high-affinity plasma membrane receptor on cardiomyocytes. In conclusion, these novel data show that FABP4 is released from human adipocytes and elicits a direct and acute Ca²⁺-dependent suppressing effect on cardiomyocyte contraction. The increased concentrations of circulating FABP4 and/or locally expressed FABP4 in epicardial fat tissue as observed in obese individuals may be partially responsible for the development of heart dysfunction in these individuals.

see glossary for definition of this term.

REFERENCE

Bile acids
Steroid acids found primarily in the bile of mammals. The 2 major bile acids in humans are cholic acid and chenodeoxycholic acid. The primary function of bile acids is to facilitate and assist micelle formation for the processing of dietary fat.

Body mass index (BMI)
A statistical measure of body weight involving an individual's height and weight. The formula to calculate BMI is: Mass (kg)/height (m²).

Brown adipose tissue (BAT)
One of the 2 types of fat found in mammals (the other and primary type in humans is white adipose tissue). BAT is abundant in hibernating animals and newborns, and its primary function is for heat generation. It appears brown in nature versus white adipose tissue because of its high mitochondrial content, which is rich in iron content.

Fatty acid-binding protein 4 (FABP4)
A member of a conserved multigene family of intracellular lipid-binding proteins having an approximate molecular mass of 15 kDa that are involved in the cellular uptake and transport of fatty acids. FABP4 is alternatively known as adipocyte FABP, is primarily expressed in adipose tissue, liver, and macrophages.

Fluoro-D-deoxyglucose ([¹⁸F]2-fluoro-2-deoxyglucose)
A glucose analogue labelled with the positron emitting isotope, fluorine-18 at the 2-position of the glucose ring. Fluoro-D-deoxyglucose is commonly used to non-invasively measure regional myocardial glucose uptake via positron emission tomography (PET). After infusion of fluoro-D-deoxyglucose, it is transported into the myocardium via glucose transporters, and is subsequently phosphorylated by hexokinase, generating fluoro-D-deoxyglucose-6-phosphate, which is not metabolized further, and thus accumulates in the myocardium.

Hexosamine biosynthetic pathway (HPB)
A percentage of fructose-6-phosphate generated by glycolysis is utilized by the hexosamine biosynthetic pathway (HPB). The enzyme glutamine: fructose-6-phosphate aminotransferase (GFAT) catalyses the irreversible transfer of the amino group from glutamine and the isomerisation of fructose-6-phosphate generating glucosamine-6-phosphate and glutamate. A series of enzymatic steps leads to the conversion of glucosamine-6-phosphate to O-linked β-N-acetylglucosamine (O-GlcNAc), the end product of the HBP, which can be attached to the hydroxyl moieties of serine and threonine residues of cytosolic and nuclear proteins.

Jun N-terminal kinase (JNK)
A member of the mitogen activated protein kinase (MAPK) superfamily that is primarily activated in response to cellular stresses. Activated JNK can phosphorylate the transcription factor, c-Jun within its N-terminal activation domain.

Toll-like receptors (TLRs)
A family of 10 receptors (TLR1-TLR10) characterized by the presence of extracellular leucine-rich repeats and an intracellular Toll/interleukin-1 receptor (TIR) domain. TLRs are implicated in host defence and inflammation as they respond to both to microbial products and endogenous factors that are released during tissue injury and inflammation.

Transmembrane G protein-coupled receptors (TGRs)
Are receptors spanning the entire plasma membrane that consists of 7 transmembrane domains. They
function in sensing molecules outside the cell in order to activate intracellular signal transduction pathways, ultimately resulting in a cellular functional response. For most part, TGRs mediate signal transduction primarily via 2 types of second messenger molecules, either cAMP or IP3 and DAG.