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Causes, Characteristics, and Consequences of Metabolically Unhealthy Normal Weight in Humans

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A BMI in the normal range associates with a decreased risk of cardiometabolic disease and all-cause mortality. However, not all subjects in this BMI range have this low risk. Compared to people who are of normal weight and metabolically healthy, subjects who are of normal weight but metabolically unhealthy (~20% of the normal weight adult population) have a greater than 3-fold higher risk of all-cause mortality and/or cardiovascular events. Here we address to what extent major risk phenotypes determine metabolic health in lean compared to overweight and obese people and provide support for the existence of a lipodystrophy-like phenotype in the general population. Furthermore, we highlight the molecular mechanisms that induce this phenotype. Finally, we propose strategies as to how this knowledge could be implemented in the prevention and treatment of cardiometabolic diseases in different stages of adiposity in routine clinical practice.

Introduction

The prevalence of overweight and obese individuals has increased globally during the last few decades, and an elevated fat mass in those with a BMI > 18.5 kg/m^2 is thought to promote morbidity and mortality (NCD Risk Factor Collaboration (NCD-RisC), 2016). While there has been considerable debate as to whether the lowest risk of mortality is actually found in the overweight population (defined by WHO as a BMI of 25.0–<30.0 kg/m^2) (Flegal et al., 2013; Hughes, 2013; Ahima and Lazar, 2013), the largest study with the most rigorous criteria to account for confounding factors recently showed that a BMI in the normal weight range (defined by WHO as a BMI of 18.5–<25.0 kg/m^2) associates with the lowest all-cause mortality (Di Angelantonio et al., 2016). Specifically, a BMI of 20.0–25.0 kg/m^2 was found to be the most protective. These data suggest that maintaining the BMI in this range may effectively reduce the risk of early death. However, does this assumption apply to all subjects in this BMI range? The research into the causes and consequences of metabolically healthy obesity (MHO) has taught us that for a certain BMI, the risk of cardiometablic disease and death can vary substantially among subjects (Karelis et al., 2004; McLaughlin et al., 2007; Wildman et al., 2008; Ahima and Lazar, 2013; Stefan et al., 2013; Blüher, 2014; Samocha-Bonet et al., 2014; Lotta et al., 2015; Mathew et al., 2016). In this respect, the largest meta-analysis showed that, compared to metabolically healthy people in the normal weight range, subjects with MHO are not at an increased risk of all-cause mortality and/or cardiovascular events (RR 1.19, 0.98–1.38) during a mean (SD) follow-up of 11.5 (8.3) years. Nevertheless, this RR increased to 1.24 (1.02–1.55) when only studies with 10 or more years of follow-up were considered, indicating that MHO may be a transient condition. Interestingly, in that analysis the highest risk was found for metabolically unhealthy individuals of normal weight (RR 3.14, 95% CI 2.36–3.93) (Kramer et al., 2013). This finding raises three important questions: (1) what phenotypes characterize these metabolically unhealthy normal weight people, (2) do these phenotypes differ from those which place obese subjects at increased risk, and (3) what molecular mechanisms determine these phenotypes in lean and in obese subjects?

Definition of Metabolic Health

Prior to addressing these questions it is important to understand what parameters are presently being used to classify a person as metabolically healthy. In some studies the absence of insulin resistance (Meigs et al., 2006; Stefan et al., 2008) or the absence of insulin resistance plus low subclinical inflammation, as determined by C-reactive protein (CRP) levels, in combination with the presence of fewer than 2 parameters of the metabolic syndrome (Wildman et al., 2008; Karelis and Rabasa-Lhoret, 2008) was proposed to represent metabolic health. However, in most studies estimates of insulin resistance and subclinical inflammation were not determined and a person was considered metabolically healthy when fewer than 2 parameters of the metabolic syndrome were present (Stefan et al., 2013; Kramer et al., 2013; Phillips, 2017) (Figure 1). The problem with these parameters is that they vary significantly and it is unclear whether elevated blood glucose, blood lipids, and blood pressure values in lean subjects are a result of the same pathophysiological mechanisms that may be active in obese subjects. Thus, it is important to determine the major risk phenotypes of metabolically unhealthy lean people and to investigate whether they differ from those of metabolically unhealthy obese subjects.

Lipodystrophy-like Phenotypes in the General Population

To approach this goal one can make use of the wealth of information deriving from studies about total and partial lipodystrophy. In

Metabolic risk criteria	Parameters and cut-offs
1.	Systolic/diastolic blood pressure ≥130/85 mm Hg or antihypertensive medication use
2.	Fasting triglyceride level ≥150 mg/dl
3.	Fasting HDL-cholesterol level < 40 mg/dl in men or < 50 mg/dl in women or lipid-lowering medication use
4.	Fasting glucose level ≥100 mg/dl or antidiabetic medication use
5.	High sensitivity C-reactive protein levels >90th percentile
6.	Homeostasis model assessment of insulin resistance >90th percentile
Metabolic health: < 2 metabolic at-risk criteria	

Figure 1. Parameters that Are Being Widely Used to Define Metabolic Risk
(1–4) Determinants of metabolic risk based on the parameters of the metabolic syndrome as defined by the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) in 2005. (1–6) Determinants of metabolic risk proposed by Wildman et al. (2008) based on data from the Third National Health and Nutrition Examination Survey (NHANES).

this respect, Abhimanyu Garg, David Savage, Stephen O'Rahilly, and others provided important information about the classification, clinical features, and molecular basis of genetic and acquired lipodystrophies (Garg, 2004, 2011; O'Rahilly, 2009; Gandotra et al., 2011; Semple et al., 2011; Patni and Garg, 2015; Robbins and Savage, 2015). Among the clinical characteristics of lipodystrophy early diabetes, severe insulin resistance and hypertriglyceridemia, hepatic steatosis, hepatosplenomegaly, acanthosis nigricans, and polycystic ovarian syndrome are commonly observed in lipodystrophy. While with an estimated prevalence of one in a million, the genetic forms of lipodystrophy are relatively seldom (Garg, 2011); in the general population some features of lipodystrophy, e.g., insulin resistance and hepatic steatosis, were also found in lean people not having been diagnosed with lipodystrophy. In this respect, Neil Ruderman, Gerald Shulman, and colleagues provided important data showing that insulin resistance and accumulation of lipids in the skeletal muscle and in the liver can be found in lean people (Ruderman et al., 1981, 1998; Shulman, 2014). While increased intramyocellular lipid levels can also be found in insulin-sensitive subjects (Dubé et al., 2008), fatty liver and increased visceral fat mass are predominantly found in insulin resistance and are associated with an increased risk of cardiometabolic diseases (Després and Lemieux, 2006; Stefan et al., 2008, 2016; Fabbrini et al., 2009). Importantly, in the Third National Health and Nutrition Examination Survey (NHANES III) persons with normal weight but central obesity, as determined by increased waist-to-hip ratio, were found to have the worst long-term survival compared to all other body composition phenotypes (Sahakyan et al., 2015). An increased waist-to-hip ratio may be an estimate of increased visceral fat mass and fatty liver and of reduced lower body fat mass. In agreement with these findings, increased femoral subcutaneous fat mass is also thought to be protective of cardiometabolic diseases and mortality. In contrast, abdominal subcutaneous fat mass is thought to increase this risk (Karpe and Pinnick, 2015). This information is supportive of the existence of specific body composition and metabolic phenotypes in metabolically unhealthy normal weight people. However, there is no systematic analysis about the prevalence of these various phenotypes in a large population.

Prevalences of Risk Phenotypes among BMI Categories

Therefore, we determined the four risk phenotypes: fatty liver, visceral obesity, high percentage subcutaneous abdominal fat mass (ratio of subcutaneous abdominal fat to total fat mass), and low percentage subcutaneous leg fat mass (ratio of leg fat to total fat mass) in a total of 981 subjects (mean age [SD] 45.0 [12.8] years, females 62%) who were at increased risk of cardiometabolic diseases based upon their weight, a family history of diabetes, a personal history of gestational diabetes (in women), or elevated glucose levels in the non-diabetic range. These subjects underwent precise phenotyping using whole-body magnetic resonance (MR) imaging and ^{1}H-MR spectroscopy measurements in the research unit of our University Hospital (Stefan et al., 2008, 2016). We also determined the presence of insulin secretion failure and insulin resistance; these factors are strong and independent predictors of incident diabetes (Lillioja et al., 1993), and furthermore, insulin resistance is involved in the pathogenesis of cardiovascular disease (Ginsberg, 2000; Saltiel and Kahn, 2001). Finally, because low cardiorespiratory fitness is an important determinant of cardiovascular disease, all-cause mortality, and various cancer mortality rates (Ross et al., 2016), and also considering that increased carotid intima-media thickness (cIMT) strongly predicts cardiovascular disease incidence (Lorenz et al., 2007), we determined these phenotypes in our population (Table S1). We considered our subjects metabolically healthy when fewer than 2 parameters of the metabolic syndrome were present (Figure 1). Notably, although these criteria have often been used in epidemiological studies to determine metabolic health (Wildman et al., 2008; Kramer et al., 2013; Eckel et al., 2015; Gujral et al., 2017), they are very crude and there is likely to be considerable heterogeneity among subjects The relationships of the phenotypes with metabolic health were similar in men and women, so we present an analysis that combines male and female subjects. In our metabolically unhealthy normal weight subjects, the most prevalent risk phenotype is insulin secretion failure (Figure 2; the respective cut-offs defining the risk phenotypes are described in the legend of the Figure 2). Compared to metabolically healthy normal weight subjects, these individuals also more frequently have insulin resistance, nonalcoholic fatty liver disease (NAFLD), visceral obesity, and increased cIMT. Interestingly, in unhealthy normal weight people, a low percentage subcutaneous leg fat mass (the adipose tissue depot which is thought to be protective of cardiometabolic diseases; Karpe and Pinnick, 2015) can be found with high prevalence. In metabolically unhealthy, overweight, and obese subjects a different picture emerges. While comparing metabolically unhealthy subjects who are of normal weight to metabolically unhealthy overweight and obese subjects, a gradual increase of the prevalence of insulin resistance (β = 0.96, $p < 0.0001$), low percentage

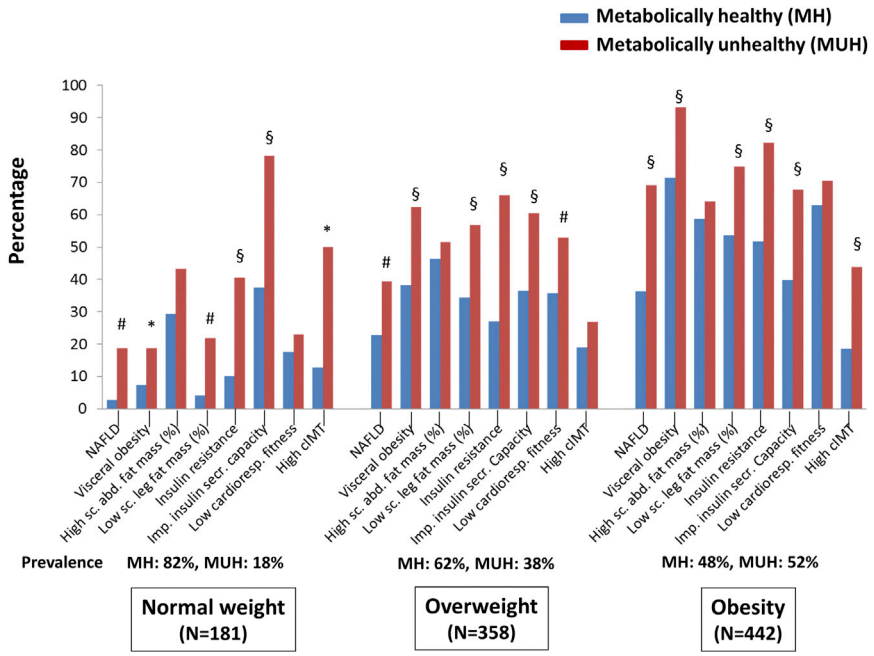

Figure 2. Prevalence of Risk Phenotypes among a Total of 981 Subjects Stratified by BMI Categories

Subjects were categorized in different BMI strata (normal weight [BMI 18.5–24.9 kg/m^2], overweight [BMI 25.0–29.9 kg/m^2], and obese [BMI ≥ 30 kg/m^2]). Nonalcoholic fatty liver disease (NAFLD) was determined with ^{1}H-magnetic resonance (MR) spectroscopy and body fat distribution with MR imaging. Insulin resistance and impaired insulin secretion capacity were measured during a frequently sampled oral glucose tolerance test. Cardiorespiratory fitness was determined on a cycle ergometer in a subgroup of 786 subjects. Carotid intima-media thickness (cIMT) was measured in a subgroup of 456 subjects with high-resolution ultrasound. Cut-off values to define at-risk phenotypes were as follows: impaired insulin secretion capacity, lower median of the disposition index (insulin sensitivity$_{OGTT}$ [10,000/√{Ins_{mean} × $Gluc_{mean}$ × Ins_0 × $Gluc_0$}] × insulinogenic index [Ins_{30} − Ins_0 / $Gluc_{30}$ − $Gluc_0$]; <1,279 a.u.); insulin resistance, lower median of insulin sensitivity$_{OGTT}$ (<9.00 a.u.); NAFLD, liver fat content$_{MRS}$ > 5.6%; visceral obesity$_{MRT}$, visceral fat mass > 4.6 kg in 368 men (corresponding to >102 cm waist circumference) and visceral fat mass > 2.0 kg in 613 women (corresponding to >88 cm waist circumference); high percentage subc. abd. fat mass$_{MRT}$, upper median ratio of subcutaneous abdominal to total fat mass; low percentage subc. leg fat mass$_{MRT}$, lower median ratio of subcutaneous leg to total fat mass; low cardioresp. fitness, lower median of VO_{2max} (<21.0 mL/kg/min); high cIMT, highest quartile of carotid intima-media thickness (cIMT). *p < 0.05, #p < 0.01, §p < 0.001 in the χ^2-test. Prevalences of the risk phenotypes based on the extreme tertiles of the continuous parameters in metabolically healthy/unhealthy (MH/MUH) subjects: high sc. abd. fat mass 20.2/31.6 (normal weight), 42.8/50.7 (overweight), 55.9/70.8 (obese); low sc. leg fat mass 2.3/22.7 (normal weight), 33.8/69.6 (overweight), 63.3/89.9 (obese); insulin resistance 4.4/30.0 (normal weight), 20.6/69.4 (overweight), 65.5/92.4 (obese); imp. insulin secr. capacity 32.0/71.4 (normal weight), 28.8/66.3 (overweight), 43.3/72.0 (obese); low cardioresp. fitness 12.5/10.5 (normal weight), 29.6/55.7 (overweight), 69.7/83.3 (obese) (N.S., F.S., H.-U.H., unpublished data).

subcutaneous leg fat mass (β = 0.99, p < 0.0001), and impaired cardiorespiratory fitness (β = 0.95, p < 0.0001) can be detected, and a stronger increase of the prevalence of NAFLD (β = 1.21, p < 0.0001) and visceral obesity (β = 2.08, p < 0.0001) are observed (Figure 2). Furthermore, the differences between the incidence rates of all of the risk phenotypes between metabolically healthy and unhealthy subjects among the three BMI categories were statistically significant (χ^2-test, all p < 0.05). For sensitivity analyses we have also investigated these relationships when more extreme values, such as those defined by tertiles, are being used to define risk phenotypes, rather than dividing subjects by the medians of the continuous parameters of insulin sensitivity, disposition index, subcutaneous abdominal fat mass percentage, leg fat mass percentage, and cardiorespiratory fitness. In this respect, the frequency of the risk phenotypes, defined by the most extreme tertiles (legend of Figure 2), and the statistical results were very similar to the data that derived from the median values of the phenotypes, which allowed inclusion of the total population. Furthermore, when the continuous values of the phenotypic parameters were compared between metabolically healthy and unhealthy normal weight subjects, the latter population had higher liver fat content (p = 0.0002), visceral fat mass (p < 0.0001), and cIMT (p = 0.01) and lower percentage subcutaneous leg fat mass (p < 0.0001), insulin sensitivity (p < 0.0001), and insulin secretion (p = 0.0002). Similar results were observed for overweight and obese subjects. Finally, we also ran sex-specific analyses and found concordant relationships in males and females. Specifically, visceral fat mass was higher (males p = 0.004; females p = 0.002) and subcutaneous leg fat mass percentage was lower for both men and women (males p = 0.008; females p = 0.005) when comparing metabolically unhealthy to metabolically healthy normal weight populations. When we performed principal component analyses to visualize the complex phenotypic relationships and to identify common patterns, we found that insulin sensitivity, insulin secretion, cardiorespiratory fitness, and subcutaneous leg fat mass correlated positively with one component. In contrast, visceral fat mass, liver fat content, and subcutaneous abdominal fat mass correlated negatively with this component and visceral fat mass and liver fat content correlated strongly with each other. Similar relationships were found in the normal weight, overweight, and obese groups (Figure 3). Notably, because we studied Caucasians, these findings only allow us to draw conclusions about such relationships in this ethnic group. In this respect, a very recent analysis from the Multi-Ethnic Study of Atherosclerosis, in which metabolic risk was defined by the same criteria that we used, the variability of incidence of being metabolically unhealthy with normal weight was very large between ethnic groups, with a prevalence of 21.0% in whites, 32.2% in Chinese Americans, 31.1% in African Americans, 38.5% in Hispanics, and 43.6% in South Asians (Gujral et al., 2017). Furthermore, we only studied middle-aged people and have no information as to whether our conclusions can be extrapolated to younger or older subjects.

This first head-to-head comparison of a relatively large number of important and precisely measured cardiometabolic risk phenotypes reveals that metabolically unhealthy lean people mainly have insulin secretion failure, insulin resistance, and

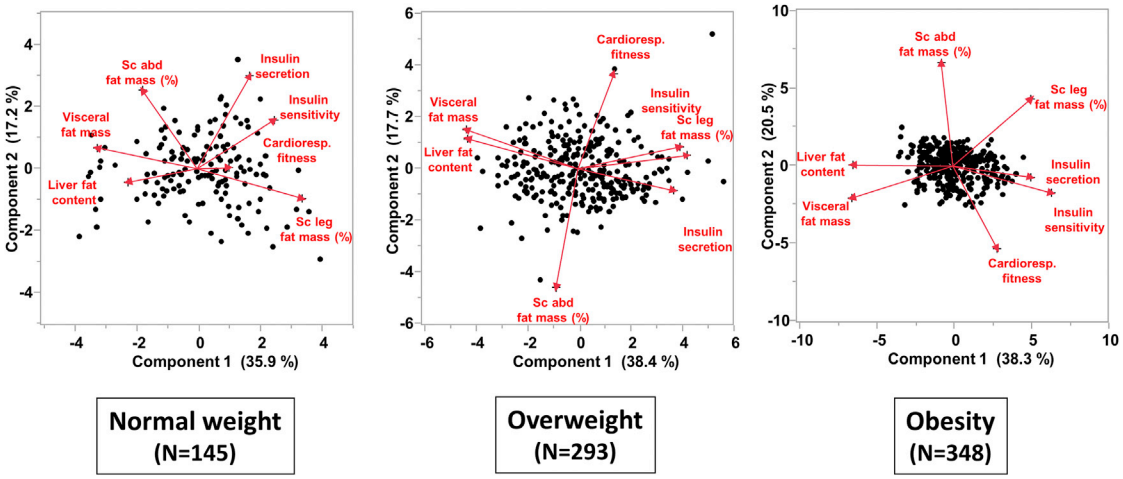

Figure 3. Principle Component Analyses of Phenotypes Stratified by BMI Categories
Depicted are the biplots in the three BMI groups that graphically displayed information on both samples and variables of the data matrix.

increased cIMT. As was expected from data in the literature, insulin secretion failure appears to be of major relevance for cardiometabolic risk in normal weight subjects, as it promotes hyperglycemia. However, possibly because of the somewhat difficult procedures to precisely measure insulin secretion, it is mostly neglected as an early predictor in the experimental and, particularly, clinical settings. In contrast, insulin resistance can easily be measured in such a framework and is a widely recognized determinant of metabolic risk (Laakso and Kuusisto, 2014). Importantly, there is accumulating evidence that, based on the tissue selectiveness in the development of insulin resistance, in the insulin-resistant state the myocardium is prone to insulin-induced metabolic stress, resulting in cardiac injury and that, via the mitogen-activated protein kinase (MAPK) pathway, hyperinsulinemia may induce atherosclerosis (Nolan et al., 2015). Furthermore, compared to metabolically healthy normal weight subjects, metabolically unhealthy normal weight subjects, as defined by a BMI <25 kg/m^2 and presence of insulin resistance, were found to have an elevated risk of colorectal cancer (OR 1.59, 95% CI 1.10–2.28). This risk was also higher than that of the other phenotypes studied in the same setting in the European Prospective Investigation into Cancer and Nutrition study (Murphy et al., 2016). These data support the hypothesis that insulin resistance and hyperinsulinemia may be important determinants not only of the cardiometabolic risk, but also of the cancer risk in normal weight subjects. Certainly, it cannot be excluded that other parameters that are closely associated with hyperinsulinemia and which have a direct carcinogenic potential, such as chronic low-grade inflammation and alterations in adipokine concentrations (Aleksandrova et al., 2013), may also be responsible for this relationship. In our population, NAFLD and visceral obesity are less prevalent in normal weight subjects. Nevertheless, if present, these subjects have an elevated risk of being metabolically unhealthy, and together with insulin resistance, NAFLD and visceral obesity are risk phenotypes that fit well to the concept of the lipodystrophy-like phenotype in the general population.

In this respect, the question arises whether data from large studies in humans can support the concept, which was predominantly developed on the basis of animal data and data from small adipose tissue biopsy studies in humans, that impaired adipogenesis, resulting in ''adipose overflow'' and consequently in ectopic deposition of lipids, is an important determinant of increased cardiometabolic risk (Danforth, 2000; Tan and Vidal-Puig, 2008; Arner et al., 2011; Tchkonia et al., 2013; Rosen and Spiegelman, 2014; Kusminski et al., 2016; Pellegrinelli et al., 2016; Smith and Kahn, 2016; Stern et al., 2016). It is not easy to test this hypothesis because of several limitations: first, with an increase of total fat mass, both visceral and, predominantly, subcutaneous fat mass increase, as was also the case in our study. Thus, it is difficult to separate the contribution of these fat depots to the regulation of metabolism. So far, studies have suggested that both subcutaneous adipose tissue and visceral adipose tissue mass positively associate with metabolic risk parameters, albeit the relationships are stronger for visceral fat mass (Fox et al., 2007; Pou et al., 2009). Second, in these studies often only subcutaneous abdominal fat mass was measured (Fox et al., 2007; Pou et al., 2009). Subcutaneous abdominal adipose tissue is divided by the Scarpa's fascia into a deep subcutaneous adipose tissue and a superficial subcutaneous adipose tissue, of which the deep adipose tissue layer has higher expression of proinflammatory, lipogenic, and lipolytic genes, contains higher proportions of saturated fatty acids, and strongly and independently associates with insulin resistance (Marinou et al., 2014). Thus, quantification of total subcutaneous abdominal fat mass, which is often done with conventional methods such as dual-energy X-ray absorptiometry (DXA), may not help to predict cardiometabolic risk. In contrast, quantification of gluteofemoral adipose tissue mass, also named leg fat mass, may be of greater value. Frederik Karpe, Keith Frayn, Leanne Hodson, and colleagues elegantly showed that the relative release of palmitoleate, the insulin-sensitizing lipokine (Cao et al., 2008; Stefan et al., 2010), was markedly higher from gluteofemoral adipose tissue compared with subcutaneous abdominal adipose tissue (Pinnick et al., 2012). Furthermore, by directly measuring adipogenesis the groups of Marc Hellerstein and Eric Ravussin recently provided important information that preadipocyte and adipocyte formation is higher in the femoral compared to the

abdominal subcutaneous adipose depot (White et al., 2016). In agreement with a beneficial role of leg fat on the regulation of metabolism, subcutaneous thigh adipose tissue mass, but not subcutaneous abdominal adipose tissue mass, weakly associated with a lower prevalence of the metabolic syndrome (Goodpaster et al., 2005). Thus, if the concept that impaired adipogenesis is an important determinant of increased cardiometabolic risk is relevant in humans, then low subcutaneous fat mass and, more specifically, low leg fat mass should predict a high metabolic risk, independently of subcutaneous abdominal fat mass, visceral fat mass, and liver fat content. When testing this hypothesis in our population, in a forward stepwise regression analysis including all of our 981 subjects, low percentage leg fat mass is the third strongest determinant of metabolic risk, after fatty liver and visceral obesity. However, when these analyses are being performed separately within the groups of normal weight and obese subjects another picture emerges. While low percentage leg fat mass, followed by fatty liver, is the strongest independent predictor of metabolic risk in normal weight subjects, it is not a significant determinant of metabolic risk in obese subjects. Although we did not measure adipogenesis, but only quantified fat mass, this finding supports the hypothesis that in normal weight people a low adipogenesis, particularly in the lower body fat compartment, may be a significant regulator of metabolism. Furthermore, while the body fat distribution of the metabolically unhealthy normal weight subjects is far from being comparable to the body fat distribution of patients with total or partial lipodystrophy, a lipodystrophy-like phenotype is detectable in this population. Notably, when calculating the ratios of visceral fat mass/subcutaneous abdominal fat mass and of visceral fat mass/leg fat mass, the median [IQR] values differ greatly between the metabolically unhealthy (0.39 [0.45] and 0.30 [0.34]) and the metabolically healthy (0.21 [0.19] and 0.12 [0.14], respectively) normal weight subjects. Such large differences in these ratios are not present in the obese subjects (metabolically unhealthy: 0.29 [0.28] and 0.30 [0.32]; metabolically healthy: 0.22 [0.17] and 0.20 [0.16]).

Molecular Mechanisms of Metabolic Risk in Normal Weight Subjects

If so, then it would be crucial to having support for this hypothesis from studies that address molecular mechanisms promoting the development of this lipodystrophy-like phenotype in the general population. In 2014, and most recently, Robert Scott, Luca Lotta, Hanieh Yaghootkar, and colleagues provided important genetic and integrative genomic information about pathways involved in the genesis of this phenotype (Scott et al., 2014; Yaghootkar et al., 2014, 2016; Lotta et al., 2017). Scott et al. (2014) selected 10 variants (in or near *IRS1*, *GRB14*, *ARL15*, *PPARG*, *PEPD*, *ANKRD55/MAP3K1*, *PDGFC*, *LYPLAL1*, *RSPO3*, and *FAM13A1*) and determined an insulin resistance score. They found that the insulin resistance score associated not only strongly with insulin resistance, but also with a lower BMI and lower total fat mass. Furthermore, among the fat compartments, the score most strongly associated with lower gluteofemoral fat mass. This insulin resistance score also associated with higher liver enzymes, while no association with lean mass measurements was found. Using a similar approach, Yaghootkar et al. (2014, 2016) recently found similar relationships in other populations. Applying an integrative genomic approach to characterize genetic and molecular mechanisms of insulin resistance at a given level of adiposity, Lotta et al. (2017) found that 53 loci strongly associated with insulin resistance, type 2 diabetes, and coronary heart disease. No differences in associations across sex or BMI strata were found. The 53 loci strongly associated with a lower percentage body fat, BMI, and hip circumference and a lower gynoid and leg fat mass (Lotta et al., 2017). Furthermore, in that study Lotta et al. (2017) showed that the knockdown of four of the putative effector genes *Irs1*, *Ccdc92*, *Dnah10*, and *L3mbtl3* in mouse OP9-K cell lines, a model suitable for mid-throughput screening of genes influencing adipogenesis, resulted in reduced lipid accumulation. However, no direct studies investigating the effects of these genes on preadipocyte differentiation or adipocyte proliferation were done. Nevertheless, these findings suggest that genetically determined insulin resistance via the identified 53 loci may in part also result from a reduced ability of expansion of adipose tissue, particularly of adipose located in the lower body.

Finally, and as was expected, in studies that set out to establish the genetic prediction of insulin resistance (adjusted for BMI variability), genes that are thought to induce insulin resistance via increased fat mass, such as *FTO* and *MC4R* (O'Rahilly, 2009), were not detected. This is of particular importance as common genetic variants in *FTO* (Fall et al., 2013) or a genetic risk score of adiposity-increasing SNPs in *FTO*, *MC4R*, and *TMEM18* (Nordestgaard et al., 2012) were found to associate with higher BMI and with higher risk of type 2 diabetes, hypertension, and heart disease. These data highlight that in order to understand the etiology behind insulin resistance and insulin resistance-associated cardiometabolic disease, the separation of adiposity-promoting from adiposity-depleting mechanisms is crucial.

Prevention and Treatment of Cardiometabolic Diseases in Different Stages of Adiposity

When it comes to the prevention and treatment of cardiometabolic diseases, the medical guideline-based recommendations should be followed. These include an adoption of a healthy lifestyle and the initiation of pharmacological treatments for elevated blood pressure, dyslipidemia, and hyperglycemia, if necessary (Eckel et al., 2014; American Diabetes Association, 2017). However, these guidelines do not provide much information as to whether and to what extent prevention and treatment should be adapted to the pathophysiology of the diseases, and whether prevention and treatment should be tailored based on the amount of fat mass and fat distribution. In our analysis, low percentage of leg fat mass, indicating impaired expansion of subcutaneous adipose tissue in the lower body, is the strongest determinant of metabolic risk among the body fat compartments in normal weight subjects, but not in obese subjects. Thus, promotion of adipocyte differentiation, e.g., using the PPARG-ligands thiazolidinediones (TZD), may be the preferred pharmacologic compound in normal weight people. This is supported by findings from studies in patients with HIV/highly active antiretroviral therapy-associated lipodystrophy (HALS). This syndrome is characterized by peripheral lipoatrophy, visceral fat accumulation, and severe forms of insulin resistance and dyslipidemia (Paruthi et al., 2013; Edgeworth et al., 2013). Treatment of patients with HALS with the TZDs rosiglitazone and pioglitazone

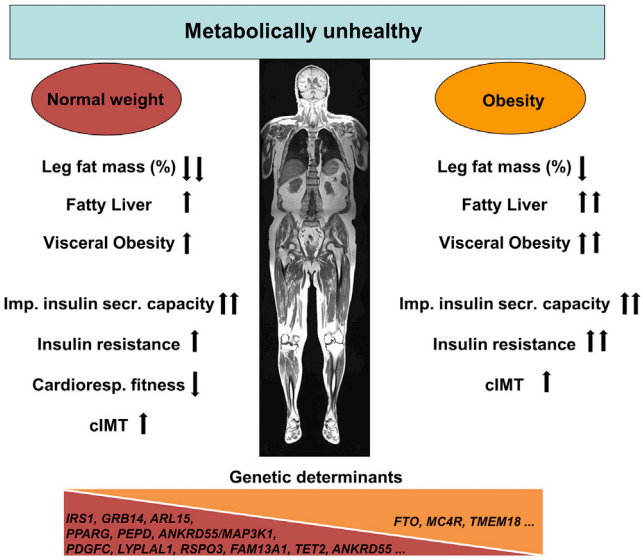

Figure 4. Phenotypes and Genetic Determinants of Metabolically Unhealthy Normal Weight and Obesity

Depicted are the phenotypes that associate with metabolic risk in normal weight and in obese subjects. The arrows indicate whether the prevalence of these phenotypes is increased or decreased in the metabolically unhealthy condition and the strength of the relationships of these phenotypes with metabolic health. Information about genetically determined pathways regulating metabolic risk via decreased and increased fat mass is given.

decreased insulin resistance and hyperlipidemia and strongly increased adiponectin levels, while no effects on the changes of fat compartments were found during a relatively short period of follow-up (Carr et al., 2004; Gavrila et al., 2005). Nevertheless, future studies need to investigate whether treatment with TZDs may be superior to other pharmacological interventions in patients with metabolically unhealthy normal weight, e.g., in the treatment of patients with type 2 diabetes and severe forms of metabolically unhealthy normal weight. In contrast, although TZDs also have insulin-sensitizing effects in obese subjects, the treatment-induced weight gain limits their use in many obese people. Of particular importance here is that, MHO, the phenotype that is also thought to be induced by TZD treatment, may be resistant to obesity-induced atherovascular complications, but not from heart failure, which strongly associates with fat mass (Mørkedal et al., 2014; Stefan et al., 2014).

While, as discussed above, impaired expansion of subcutaneous adipose tissue, particularly in the lower body, may be an important target to reduce the increased cardiovascular risk, it may not be sufficient to improve impaired insulin secretion, which is very prevalent in our normal weight subjects. In our population, a low percentage of leg fat mass strongly associates with insulin resistance; however, it only weakly associates with impaired insulin secretion. Nevertheless, treatment with the TZD pioglitazone also reduced the diabetes risk and improved insulin secretion in non-obese subjects with impaired glucose tolerance (DeFronzo et al., 2011). Unfortunately, in that study no analysis was performed in normal weight individuals. Based on the fact that TZDs also have direct beta cell protective effects in respect to their function and survival (Shimabukuro et al., 1997), these drugs may also improve beta cell function in normal weight subjects with hyperglycemia.

Incretin-based treatments may be more effective in overweight and obese subjects than in normal weight individuals. Glucagon-like peptide-1 (GLP-1) response to oral glucose is reduced in overweight and obese subjects, independent of the status of glucose tolerance (Færch et al., 2015). Furthermore, in clinical trials the improvement of hyperglycemia and dyslipidemia, which was observed during treatment with GLP-1 receptor agonists, was strongly associated with weight loss (Meier, 2012). In addition, in the Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes (LEADER) study, which included 9,340 patients, treatment with the GLP-1 receptor agonist liraglutide was associated with lower incidence of the primary composite outcome in obese, but not in non-obese, patients with type 2 diabetes (Marso et al., 2016). Nevertheless, because GLP-1 also has direct beneficial effects on glycemia, inflammation, lipidemia, and cardiovascular physiology (Drucker, 2016), trials longer than the LEADER study may also reveal cardioprotective effects of GLP-1 treatment in non-obese patients.

Conclusion

Considering the very high risk of cardiometabolic disease, colorectal cancer, and mortality in metabolically unhealthy normal weight subjects, it is important to understand what phenotypes characterize this population. In this regard, we have summarized published information and provided data indicating that in lean subjects elevated glucose, dyslipidemia, and hypertension—the parameters that are commonly used to determine the metabolic risk—are more strongly associated with a relatively low leg fat mass than with high subcutaneous abdominal fat mass, visceral obesity, or fatty liver. This finding provides information that a lipodystrophy-like phenotype exists in the general population. In addition to the abnormalities in lipid storage, this phenotype is also strongly characterized by impaired insulin secretion capacity and by insulin resistance, low cardiorespiratory fitness, and increased cIMT. While most of the latter parameters also determine the metabolic risk in obese subjects, among the body fat compartments and fatty liver, disproportionate lipid storage in the lower body is not independently associated with their metabolic risk. Furthermore, genetic analyses suggest that metabolic risk appears to be determined by different pathways in normal weight and obese subjects (Figure 4). These findings may have several implications for clinical interventions and for drug development. First, in the case that a subject with normal weight may have two or more parameters of the metabolic syndrome in a clinical examination, it would be important to determine whether impaired glucose tolerance, fatty liver, or early atherosclerosis is present, so the early treatment of these conditions can be implemented. Second, in respect to the improvement of hyperglycemia and dyslipidemia in normal weight individuals, drugs that can promote adipocyte differentiation may be most effective, when it comes to pharmacological intervention. Third, concepts of drug development directed toward the expansion of adipose tissue may prove to be promising to treat not only metabolically unhealthy lean people, but also overweight and a subset of obese people. Fourth, applying well-defined phenotyping strategies in clinical trials to better separate the metabolic risk in normal weight and obese subjects

will help to more precisely understand the pathophysiology of cardiometabolic disease in that targeted lifestyle and pharmacological intervention can be implemented to accomplish the goal of providing personalized medicine to our patients.

SUPPLEMENTAL INFORMATION

Supplemental Information includes Supplemental Experimental Procedures and one table and can be found with this article online at http://dx.doi.org/10.1016/j.cmet.2017.07.008.

AUTHOR CONTRIBUTIONS

All authors contributed to the research of the published work, analyzed data, and wrote parts of the paper.

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