Is Visceral Fat Reduction Necessary to Favour Metabolic Changes in the Liver?

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Abstract

As excess body weight constitutes a major health problem, it is now important for hepatologists to weigh risk factors that lead to insulin resistance and hepatic steatosis. This mini-review focuses on the type of bodily fat distribution that determines the ectopic fat storage into the liver in overweight or obese people. Although obesity is closely associated with non-alcoholic fatty liver disease, the excess of visceral fat storage is reckoned to be just as or even more important.

Abbreviations

NAFLD: non-alcoholic fatty liver disease; BMI: body mass index; NASH: non-alcoholic steatohepatitis; MS: metabolic syndrome; VAT: visceral adipose tissue; SAT: subcutaneous adipose tissue; LA: liver attenuation; FFA free fatty acids; TNF-α: tumor necrosis factor-alpha; IL-6: interleukin-6; UCP: uncoupling protein.

Introduction

Obesity predisposes to several serious medical conditions, including the spectrum of liver abnormalities collectively referred to as non-alcoholic fatty liver disease (NAFLD) [1–8]. The global obesity pandemic so evident in the Asia–Pacific region underlies a significant increase of NAFLD over the past decades, so that NAFLD has become the most frequent cause of liver disease in most countries [8–10]. There has been a perception that some Asian patients who have NAFLD are not obese [10], but this may depend partly on the problems of ethnic-specific definitions of overweight and obesity [11, 12]. Conversely, not all obese subjects have NAFLD [13, 14]. What is becoming apparent is that not all body fat is evil; some deposits are metabolically unhealthy, others are not! [15–17].

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Relative body weight

There is a strong curvilinear relationship between body mass index (BMI) and relative body fat mass. For this reason, BMI is widely used to define overweight and obesity, although appropriate adjustments must be considered for gender and ethnicity [11, 12]. Contemporary clinical and epidemiological studies from China, Japan and Korea indicate that fatty liver is more often associated with obesity than with alcoholism (although the latter remains important!) [8–10, 18]. There is also a direct association between BMI, extent of hepatic steatosis, non-alcoholic steatohepatitis (NASH), and advanced liver fibrosis [5, 6, 8]. Overall, approximately 75% of obese subjects have steatosis, approximately 20% have NASH, and only approximately 2% have cirrhosis [8]. The invariable relationship between NAFLD and insulin resistance, and the close nexus between NAFLD and metabolic syndrome (MS) have already been discussed [19,20]. It is now important to understand what is it about cases of obesity that leads to insulin resistance and hepatic steatosis, because not all obese subjects are metabolically unhealthy [21]. One factor that modifies NAFLD risk is recent weight gain [8]. Weight gain of 5 kg or more since the ages of 18 to 20 years in both sexes also increases the risk of developing diabetes, hypertension, and coronary heart disease, and the risk of these conditions increases with the amount of weight gained [8]. In light of the close ties between NAFLD and MS [19], weight gain would be expected to increase the risk of NAFLD; this occurs even among some apparently ‘lean’ individuals [8]. Conversely, even a very modest reduction in BMI (less than 5% of initial weight in the past 6 months) can reduce the size of selected fat depots, as reflected by improved liver function

tests in obese patients [5–9, 22]. With moderate weight loss, whether achieved by 'lifestyle intervention' (the combination of increased physical activity and dietary adjustments) or by bariatric surgery, improvement in NAFLD is impressive [9, 20, 23-25]. Improved aerobic fitness also decreases risk of developing obesity-associated complications [4]. Of interest to the present discussion, a higher level of habitual physical activity is associated with lower intra-hepatic fat content [26].

Body fat distribution

It should be emphasized that the distribution of adiposity (fat storage tissue) may be more important to ectopic fat accumulation into the liver (steatosis) than the total adipose mass [8]. Obese persons with excess visceral adipose tissue (VAT), or abdominal obesity, are at higher risk for MS components than those whose fat is located predominantly in the lower body, subcutaneously [4, 17]. Further, 'lean' NASH patients usually have abdominal obesity, or more VAT [4, 8]. Waist circumference is highly correlated to VAT and, therefore, should now be used as a surrogate marker for abdominal obesity; such has been recommended by the Asia–Pacific Guidelines on NAFLD [7]. A recent elegant study has shown that *ob/ob* mice, that are genetically predisposed to obesity, type 2 diabetes, MS and fatty liver, can be rescued from all these metabolic complications by expression of an adiponectin transgene [16]. The biological effect of such forced expression of adiponectin was to expand the subcutaneous adipose tissue (SAT) mass [16]. The observation that increasing adiposity in this adiponectin-transgenic ob/ob mouse protects against fatty liver and MS when fat distributes into its physiological storage sites (under the skin!) is consistent with the proposal that fat only distributes into the liver and other non-physiological sites (skeletal and cardiac myocytes, pancreatic beta-cells) when access to SAT becomes restricted – that is, when it is full up! [4, 16]. This conclusion is given further support by the observation that persons with morbid obesity and a high ratio of central adiposity (VAT) to total body fat have an increased risk of fatty liver and MS rather than those with lower ratios [14].

Clinical and epidemiological studies using waist circumference to estimate VAT mass find a direct association between abdominal fat and liver fat content, independent of total adipose mass and BMI [8, 14, 27, 28]. Further, several recent studies have adopted imaging methods to demonstrate that VAT rather than subcutaneous abdominal fat (i.e., SAT) is more influential than BMI in terms of predicting the presence of NAFLD [14, 27–31]. In one such study, obese subjects with hepatic steatosis had higher ratios of truncal-to-total body fat compared with similarly obese persons without fatty liver [28]. However, the sensitivity and specificity of available imaging methods for measuring liver fat content are unsatisfactory compared to [1H]-magnetic resonance spectroscopy; and the latter modality is usually not available outside a research setting [15, 26, 29–33]. Conflicting results on the accuracy of different modalities have been reported, which may be related both to the inadequacy of 'gold standard' (liver biopsy, also burdened by conspicuous sampling errors, is rarely performed in this experimental context), and to technical factors [31-33].

Liver attenuation (LA) by computed tomography is a validated quantitative measure that is inversely related to liver fat burden. Race and sex differences on the distribution of LA, corresponding to one of the first stages of NAFLD, and the predictors of these mean differences in European American and African American participants of the Family Heart Study were examined [34]. In this study, findings confirm that there are important sex differences and race by sex interaction effects on the distribution of LA, the prevalence of NAFLD, and on the influence of metabolic risk factors on LA and NAFLD [34].

Visceral adipose tissue is a key pathogenic fat depot in the MS, but ectopic fat storage into the liver (LF) may also play an important role. It evaluates associations of VAT and LF with MS in normal weight, overweight, and obese men and women [35]. VAT and LF were associated with MS independently of each other, and these relationships were modified by BMI class such that VAT was the more important depot at lower levels of obesity and LF at higher levels [35]. Importantly, NAFLD is accepted to be a metabolic risk factor in overweight and obese individuals.

Ethnicity and gender

Obesity-associated health risks are also influenced by ethnicity and gender. Asians generally have a higher percentage of body fat and VAT than Caucasians of the same age, sex and BMI [4, 8, 11, 12]. It therefore seems logical that lower cut-off values for BMI and waist circumference would be appropriate for Asian populations. This has been recommended by the International Diabetes Federation [12], but not by a WHO Expert Committee [11]. A practical definition of obesity would ideally be based on the relationship between BMI and health outcome, rather than simply on body composition [4, 7, 8, 12]. In this respect, there appears to be a higher percentage of patients with NAFLD who are non-obese among Asians compared to their European counterparts [8]. The impact of gender on BMI-related fatty liver is partly due to the difference in relative fat content, but also depends on the distribution of body fat [8]. Women typically have a lower body distribution of adipose tissue (gyneic pattern), characterized by peripheral subcutaneous adipose tissue (SAT) deposition in the gluteofemoral region. The latter means that the ratio of SAT to muscle area in the thigh is higher in women than men. Men have a different pattern of adipose distribution (android pattern), characterized by a higher proportion of fat in intra-abdominal regions or VAT, and lower ratio of SAT to thigh muscle area [4, 17].

Thus, the capacity (or restrictiveness) of peripheral fat deposits may influence the proclivity to visceral adiposity and, thereby, exert an opposite effect on the development

of fatty liver and other metabolic complications (protects vs facilitates) [32-33].

Genetic polymorphisms

As already mentioned, more than two-thirds of obese individuals develop hepatic steatosis, but only a minority develop NASH and cirrhosis. This raises the question regarding which factors determine whether a patient is 'at risk' for developing more complicated forms of NAFLD. The distribution of lipid stores in the body discussed above may be important, because free fatty acids (FFA) arising from active lipolysis of the portal venous drainage area adipocytes (VAT) are taken up by the liver to become the major source of lipids contributing to hepatic triglyceride stores in NAFLD [5, 14, 20, 36, 37]. The functional differences between the visceral and the subcutaneous adipocytes may be related to their anatomical location. VAT and its adipose-tissue-resident macrophages produce more pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) and less adiponectin. These cytokine changes induce or compound insulin resistance [20], and play a major role in the pathogenesis of hepatic steatosis and subsequent fibrosis [5, 6, 14, 17]. An attractive hypothesis is that polymorphisms in genes which influence the release of adiponectin, or elaboration of TNF-α and IL-6, contribute to phenotypic differences in NAFLD, and this is particularly why some cases develop NASH complicated by hepatic fibrosis [5, 6, 14, 16, 20, 37].

Furthermore, the UCP1 (AG+GG) genotypes and low adiponectin levels could predispose to a more severe liver steatosis independently of MS presence. Based on our data, polymorphic UCP1 (AG+GG) obese patients with low adiponectin levels appear to be high-risk subjects for worsening of liver steatosis, a NAFLD, possibly requiring a second-step evaluation by liver biopsy [38].

Future directions

Obesity is strictly associated with NAFLD, but the distribution of excess bodily fat storage may be just as or even more important. In particular, VAT is the most important factor for the development of hepatic steatosis, independent of total adipose mass, whereas subcutaneous fat storage capacity is protective [4, 8, 17, 36, 37]. Gender, age and genetic factors are likely to influence the bodily distribution of fat. As demonstrated in transgenic mice [16] and in humans treated with 'glitazones', peroxisome proliferator-activated receptor (PPAR)g agonists which promote differentiation of pre-adipocytes to expand SAT, the redistribution of fat from visceral to peripheral subcutaneous storage sites has the potential to correct fatty liver and MS [36, 37, 39, 40]. These findings also support the portal hypothesis, where FFA and other factors released from VAT contribute to increased hepatic lipid stores, to inflammatory recruitment and, likely, to hepatic and peripheral insulin resistance [5, 6, 14, 20]. Other researchers disagree on the exclusive role of VAT in determining MS [41] and consequently NAFLD.

More carefully conducted longitudinal genetic studies are needed to obtain additional information on how and why variations occur in different lipid stores (VAT and SAT), and the relationship of these changes to the development of NAFLD/NASH, diabetes and MS. It is already known that high VAT and high liver fat content are associated with resistance to lifestyle intervention [30]. It therefore seems evident that efforts to prevent or correct NAFLD should be directed at reducing VAT stores during the earliest stages of their development, as indicated by recent weight gain and detected by increased waist circumference [7, 8, 23]. Early intervention has the greatest potential to decrease liver fat and reduce the risk of obesity-related metabolic problems [4, 7, 8, 23, 42].

Future studies are required to determine the entity of visceral fat reduction necessary to induce favourable metabolic changes in the liver. In the meantime, responsible physicians should advice patients suffering from NAFLD to modify their *apple* shape and convincing obese subjects that losing weight will do them a great deal of good.

Conflicts of interest

None to declare.

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