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Fat cell turnover in humans

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ABSTRACT

Obesity is a condition where excess body fat accumulates to such an extent that one's health may be affected. Owing to the cardiovascular and metabolic disorders associated with obesity, and the epidemic of obesity facing most countries today, life expectancy in the developed world may start to decrease for the first time in recent history. Other conditions, such as anorexia nervosa and cachexia, are characterised by subnormal levels of adipose tissue and as with obesity lead to morbidity and mortality. Given the significant personal and economic costs of these conditions and their increasing prevalence in society, understanding the factors that determine the fat mass is therefore of prime interest and may lead to effective treatments and/or interventions for these disorders. Fat mass can be regulated in two ways. The lipid filling of pre-existing fat cells could be altered and the number of fat cells could be changed by the generation of new fat cells or the dying of old ones (i.e. adipocyte turnover). This review summarizes what is known about fat cell turnover in humans and the potential clinical implications.

1. Adipocyte turnover

Whilst homeostatic mechanisms within the body work to keep the energy balance close to zero, a positive energy balance results in an increase in energy storage in cells in the form of fat (triglyceride). Similarly, a negative energy balance results in a decrease in fat storage and decreased fat cell (adipocyte) volume. Despite daily fluctuations in the energy balance, humans manage to keep the fat mass remarkably constant throughout adult life. If however, changes in the energy balance occur over time, then a net change in the corresponding fat mass occurs.

Many studies have shown that significant weight loss in humans (corresponding to a significant loss of fat tissue mass) over months or years results in a decrease in the volume of adipocytes, but no decrease in adipocyte number [1,2]. Also involuntary weight loss, such as in cancer cachexia, causes a decrease in adipocyte size without a change in number [3]. Complementary studies looking at weight gain over several months show that significant weight gain in adulthood is associated with significant increases in adipocyte volume, but similar to weight loss, no nett change in adipocyte number [4]. These results, and others, have promoted the view that weight change in adulthood is primarily the result of changes in adipocyte volume.

Given that in adulthood adipocyte number stays constant, and weight changes are predominantly accompanied by changes in adipocyte volume, one may conclude that at some critical point in development the final fat cell number is attained and after this point no fat cell turnover occurs. Analysis of adipocyte turnover using carbon-14 dating (for a detailed methodological description, see Ref. [5]), however, has recently shown that this is not the case, but rather that adipocytes are a dynamic and highly regulated population of cells. New adipocytes form constantly to replace lost adipocytes, such that approximately every 8 years 50% of adipocytes in the human subcutaneous fat mass are replaced [1].

Adipocyte progenitor cells (pre-adipocytes) originating from the stromovascular fraction of adult adipose tissue can be stimulated to proliferate and differentiate into mature cells *in vitro*. Recently, white adipose tissue progenitor cells, located in the perivascular compartment of white adipose tissue, were identified *in vivo* (for a review see Refs. [6,7]) and shown to be capable of reconstituting the adipocyte mass in lipodystrophic mice (mice with significantly decreased fat mass) [8–10]. Necrotic and apoptotic adipocytes are also found in adult human white adipose tissue [11], even though no decrease in adipocyte number is seen with age. Together these data suggest that pre-adipocytes are recruited to become lipid-filled mature adipocytes at the same rate that adipocytes die, and that in this way the fat mass is in constant flux, and adipocyte number is kept constant.

2. Adipose cellularity and weight loss

White adipose tissue has been shown to produce a number of factors that act locally or centrally to regulate energy homeostasis, and thus the fat mass. Some of these factors include circulating factors

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such as metabolites and hormones, as well as paracrine and autocrine factors, such as IGF-1 and TNFα. These factors and others (for example, sympathetic neural input has also been shown to regulate adipocyte proliferation), work in concert to maintain levels of adiposity. Recent studies suggest that TNFα in human adipose tissue serves as an important regulator of fat cell size and number in healthy subjects [12]. For a complete review of all the factors regulating energy homeostasis the reader is referred to reviews [13–15].

One well characterised factor known to play a vital role in the regulation of body energy balance is the hormone leptin. Leptin is a hormone produced by adipocytes that functions both centrally and locally to alter the metabolic status to favour energy expenditure over energy storage. Circulating leptin levels are linked to adipocyte size, such that large adipocytes produce more leptin than small adipocytes. Increased levels of leptin then act on the brain (hypothalamus) to decrease food intake and increase energy expenditure [16]. In this way circulating levels of leptin correspond to levels of adiposity. Despite this, an attenuated response to leptin in the obese state has been observed. Leptin availability to the brain decreases at high leptin concentrations due to a decrease in leptin transport across the blood–brain barrier, and leptin's ability to initiate cell-signalling cascades within the brain also decreases [15,16]. In contrast to this, dramatically reduced levels (or complete lack) of leptin causes hyperphagia, reduced energy expenditure and profound obesity in animals and humans. Leptin is just one of many signalling events that occur in response to a decrease in adipocyte size, putting pressure on the fat cell, via the brain, to restore 'normal' fat cell volume. Indeed, there is a very strong correlation between the size of fat cells and the production as well as secretion of leptin in human adipose tissue [17]. In addition to this, smaller adipocytes turnover triglycerides at a slower rate than large adipocytes [18], resulting in decreased energy expenditure of small adipocytes compared to large adipocytes (since triglyceride turnover is an energy-wasting process).

Thus, taken together, the lack of ability to lose adipocytes following significant weight loss, the increased fat-filling drive resulting from smaller adipocytes, and the decreased energy expenditure of smaller adipocytes compared to larger adipocytes, may explain why the success rate in keeping weight off following significant weight loss in obese individuals is so poor (greater than 90% of individuals who lose weight on dietary/life style regimes will regain the weight, or more).

3. White adipose tissue cellularity

The fat mass in humans is the product of both adipocyte volume and adipocyte number. Objectively, obesity has been defined as having a body mass index of 30 or more (calculated by dividing weight in kilograms by height in metres squared). Obesity can be characterised into two main types, hyperplastic (increase in adipocyte number) and hypertrophic (increase in adipocyte volume). Obese and overweight individuals may exist anywhere along the cellularity scale, however on average certain trends appear. Hypertrophy, to a degree, is characteristic of all overweight and obese individuals. Hyperplasia, however, is correlated more strongly with obesity severity and is most marked in severely obese individuals [19] (Fig. 1). From this relationship it is tempting to conclude that as an individual increases his/her body fat mass, so does his/her adipocyte number. Fat tissue cellularity data, however, has almost exclusively been collected cross-sectionally, and therefore gives no direct information on what happens when an individual significantly increases his/her adult weight over a protracted time period. One can not rule out that prolonged periods of weight gain in adulthood may result in an increase in adipocyte number. Indeed, animal studies suggest that increases in adipocyte size precede increases in adipocyte number.

This 'critical fat cell size' hypothesis postulates that the achievement of a specific mean fat cell size triggers a subsequent increase in fat cell number. Whether, and to what extent this occurs in humans, is unknown and long-term longitudinal studies are needed in order to assess this. Therefore, at present, it is impossible to conclude whether the average increase in adipocyte number seen in obese and severely obese individuals is the result of adult adipocyte recruitment or rather a reflection of a population of people predisposed (by their pre-adulthood fat cell number) to be become obese/severely obese. In support of the latter, short-term studies in adult humans do not show any increase in adipocyte number following significant weight gain [4]. In addition, hyperplastic obesity is often linked to early-onset obesity. It is during this period fat cell number increases and the extent to which this occurs is strongly linked to adult fat cell number.

Irrespective of whether man can acquire additional fat cells in adulthood, it is clear that fat cell number does not decrease in adulthood, even following long-term weight loss. In line with this, hyperplastic obese individuals have a poorer treatment outcome following diet-induced weight loss than hypertrophic individuals (when controlled for fat mass). Often for hyperplastic obese individuals, treatments other than diet and exercise are necessary if substantial and permanent weight loss is to be achieved. Successful, but invasive therapies include surgery to reduce the amount of calories ingested (e.g. gastric bypass) and/or surgical removal of fat tissue (e.g. reconstructive surgery or liposuction). The recent discovery of a high turnover of adipocytes in adult human white adipose tissue (approximately 10% annually) now establishes an additional therapeutic target for the pharmacological intervention of obesity [1]. Understanding the mechanisms that control adipocyte turnover *in vivo* may lead to interventions that affect the adipocyte birth–death balance so as to achieve changes in the body fat mass (Fig. 2).

Adipocyte turnover is not only important for regulating the total fat mass but also for the morphology of human adipose tissue. Using the carbon-14 dating method (5) we recently found that adipocyte turnover is important for the development of hyperplasia and hypertrophy. Decreased adipogenesis and relative adipocyte death rate were demonstrated in hypertrophic compared to hyperplastic individuals [20]. Furthermore, there was a strong correlation between adipose morphology and total fat cell number in the body. Subjects with hypertrophy have a significantly lower number of adipocytes than those with hyperplasia, independent of the total fat mass [20]. The morphology of adipose tissue has a clear clinical relevance. In a large population based sample, hypertrophy was associated with decreased insulin sensitivity – even in lean and apparently healthy subjects [20]. In addition adipose hypertrophy might be diabetogenic, with two independent prospective studies showing that adipose hypertrophy is an independent risk factor for developing type 2 diabetes [21,22].

4. Tipping the birth–death balance?

Cell death of fat cells in white adipose tissue occurs primarily by necrosis-like cell death. Unlike apoptotic cell death, where cells die in a controlled non-inflammatory manner, necrosis (and necrosis-like cell death) involves macrophage recruitment and a subsequent inflammatory response. Necrosis-like cell death and associated macrophage recruitment/activation is increased in individuals with increased adipocyte size and body mass index, and has been implicated in the metabolic complications of obesity [11,23].

Whilst studies *in vitro* have identified a number of factors that appear to regulate adipocyte death and pre-adipocyte proliferation and differentiation (for example, resveratrol has recently been shown to induce adipocyte death and inhibit adipogenesis in a fat cell line [24]) very little is known about the *in vivo* situation

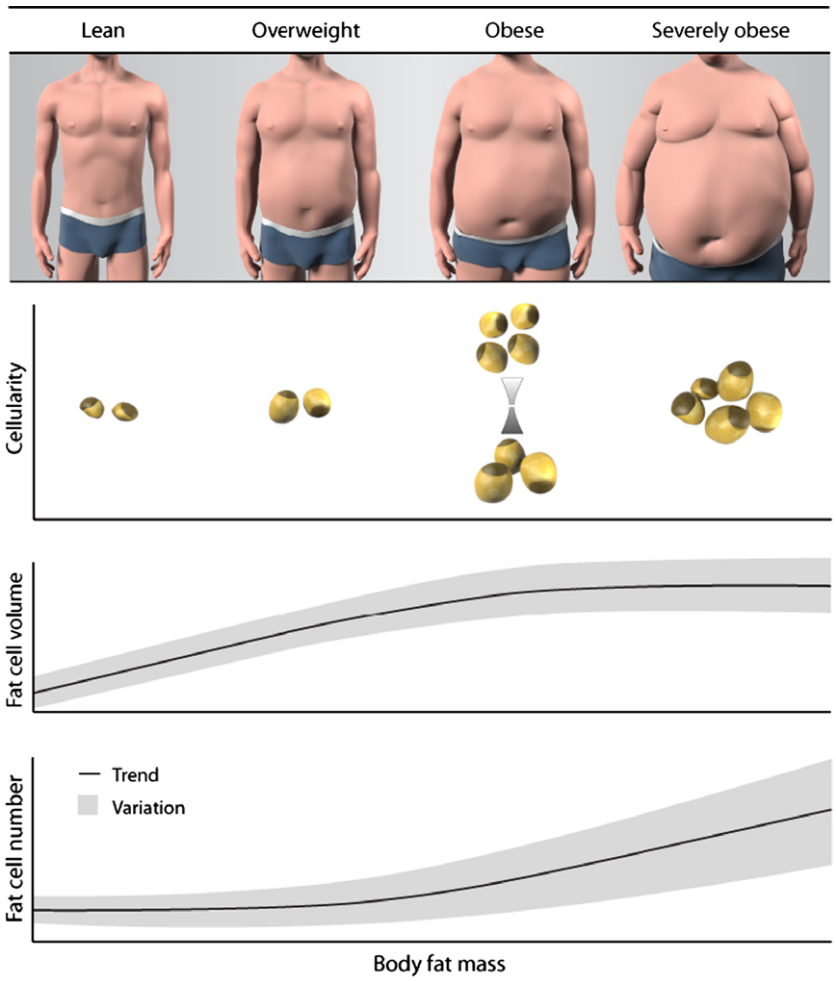

Fig. 1. Adipose cellularity in lean and obese states. The fat mass in humans is the product of fat cell number and fat cell size. Hypertrophy occurs across all obese states. Overweight individuals have on average, larger adipocytes than lean individuals, without marked changes in adipocyte number. Obesity is characterised by both larger adipocytes and more adipocytes, than lean individuals. Obesity can be characterised into two main types, hyperplastic (shown in the plot as the top group of adipocytes under obese individual) and hypertrophic (shown as the bottom group of adipocytes under the obese individual). However, as obesity increases in severity, hyperplasia becomes most evident.

in humans. Additional studies are needed to determine if decreasing the fat mass by increasing adipocyte death stimulates an inflammatory response, resulting in a worsened state of health. Whether the brain/body responds to adipocyte death by increasing pre-adipocyte proliferation and/or differentiation (in an attempt to maintain the fat mass) is unknown.

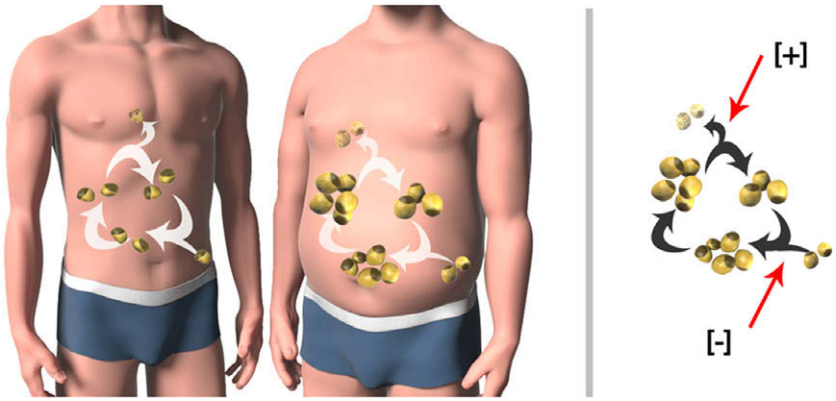

Fig. 2. Dynamics of the fat mass in lean and obese individuals. In both lean and obese individuals, adipocyte loss is balanced by adipocyte replacement (primarily believed to be by the recruitment and differentiation of pre-adipocytes into mature adipocytes). Even though, on average, obese individuals have twice the number of fat cells as lean individuals, the rate of cell turnover (i.e. the proportion of adipocytes turning over relative to the total number of adipocytes) is the same for both groups. The high turnover of adipocytes establishes a new therapeutic target for pharmacological intervention in obesity, where a change in the fat mass may be achieved by increasing adipocyte death (+) or decreasing adipocyte formation (−).

An additional point to take into account, when looking at adjusting adipocyte birth and/or death rates, is adipose tissue cellularity. Many of the metabolic complications associated with obesity are directly related to adipocyte volume. When controlled for fat mass, hypertrophic individuals have a worse metabolic profile than hypercellular individuals [25]. If one decreases his/her fat mass by increasing adipocyte death and/or decreasing adipocyte production, with no subsequent change in diet or exercise, existing adipocytes will be forced to take on the extra lipid. The resulting increase in average adipocyte volume will increase the individual's likelihood of developing metabolic disease. One scenario, where manipulating the birth–death balance could be of therapeutic interest would be cases where hyperplastic obese individuals have successfully decreased their fat cell mass by decreasing adipocyte volume, however they are limited in achieving further weight loss, or maintaining their weight loss, due to having an excess number of adipocytes. Tipping the balance in favour of reducing the number of fat cells, in parallel with diet and exercise, could re-set the individual's fat mass to a healthier level.

5. Conclusions

Obesity is a condition characterised by having an excess of fat cells which are increased in size relative to lean individuals. Traditional weight loss regimes, such as diet and exercise, are successful in decreasing adipocyte size, but fail to reduce adipocyte number. Since many obese and almost all severely obese individuals have more than the average number of adipocytes, methods other than diet and exercise alone are needed if one hopes to reduce (and maintain) the fat mass to lean levels. The dynamic and highly regulated turnover of adipocytes in adult humans establishes a new therapeutic target whereby pharmacological intervention may potentially tip the balance in favour of weight loss, or gain, depending on the preferred outcome.

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