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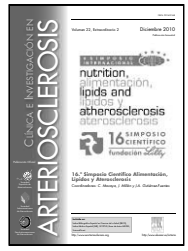

16.º SIMPOSIO CIENTÍFICO ALIMENTACIÓN, LÍPIDOS Y ATEROSCLEROSIS

Turnover of human adipocytes. Mechanisms and clinical consequences

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Introduction

The adipose mass can expand, by filling pre-existing fat cells with more lipids, by generation of new fat cells through adipogenesis or both. In humans there is continuous generation of new fat during the whole life span. Adipocyte progenitor cells such as pre-adipocytes or mesenchymal stem cells in adipose tissue can be differentiated to fat cells. There is both apoptosis and phagocytosis of fat cells in adult human adipose tissue. Stable isotopes that are given orally are incorporated into DNA of human fat cells. These data together indirectly speak for important turnover of human fat cells. A method to measure the age of fat cells in humans was recently developed by utilizing the incorporation of atmospheric ^{14}C into the DNA of fat cells. With the aid of this method it is possible to directly study adipocyte human in vivo. About 10% of the total fat cell pool is renewed every year due to constant generation of new fat cells in adults. This production is counterbalanced by an equal rate of fat cell death keeping the total amount of fat cells constant overtime in adulthood even after marked body weight reduction. The turnover process is two-fold accelerated among obese subjects in spite of the same relative death rate of old fat cells as lean subjects. It is possible that marked ongoing adipogenesis in adult humans is not only important all factor for weight gain and difficulties in retaining weight loss after slimming. It may also have implication for the cellularity of adipose tissue. Subjects with adipose hyperplasia (few large fat cells) are more at risk of developing metabolic syndrome, cardiovascular disease and type 2 diabetes than those with many small adipocytes (adipose hyperplasia).

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Background

The total mass of adipose tissue varies in subjects from 10-20 kilo in the normal state to several hundred kilos in subjects with severe obesity. The adipose mass can be reduced from excessive obesity to normal a few years after bariatric surgery. How is this plasticity of adipose tissue possible? The adipose tissue mass can expand in two different ways[1]. Pre-existing fat cells can accumulate more lipids so the volume of the cells increases. Alternatively, new fat cells are made from progenitor cells in the stroma of adipose tissue such as mesenchymal cells or already committed precursor cells (pre-adipocytes). Adipogenesis has previously been difficult to measure in vivo due to lack of adequate methods. It became possible to get some information during in the 1970's because of the introduction of measurements of the lipid weight of the fat cells[2]. By dividing the total fat mass in the body by the average weight of fat cells in the body it is, thus possible, to obtain a robust measurement of how many fat cells there are in the body.

Thanks to development in methodology the last decade we have get a much better insight in human adipogenesis. Preadipocytes cells from the adipose tissue can be isolated, proliferated and differentiated into fat cells and this differentiation of adipocyte progenitor cells is influenced by the body weight status of the donor[3]. Using chemical methods to assess cell survival there is evidence of ongoing apoptosis and cell death in human adipose tissue[4,5]. Subjects can be given stable isotopes orally. Thereafter fat cells are isolated from the tissue to study if the stable isotopes are incorporated into the DNA of the fat cells[6]. These cells can only incorporate the isotope into its DNA during ongoing cell division. Such studies do demonstrate isotope incorporation into adipocyte DNA in vivo. The studies reviewed above

indicate that there is indeed ongoing adipogenesis and fat cell death in adult humans. However, the investigations do not allow quantifaction the different aspects of adipocyte turnover such as the generation rate of new fat cells and the death rate of already existing fat cells.

Measurement of fat cell age in vivo

It is now possible to accurately determine the age of living cells in humans by utilizing the incorporation of radioactivity from the atmosphere into the DNA of the brain cells[7]. The 1950's extensive atomic bomb tests generated a marked increase in the ^{14}C content of the atmosphere. After stopping the bomb test the fall in atmospheric content of ^{14}C is exponential during the last decease which creates equilibrium of radioactivity between the atmosphere and in living organisms on earth. Fish, cattle crop and the grass all contain ^{14}C. Therefore all what we eat will contain ^{14}C. By measuring ^{14}C in cell DNA and setting it in relation to the dynamic changes in atmospheric ^{14}C content before and at time of sampling mathematical methods can assess the actual age of the cell. If cell age is younger than the subjects age there is an ongoing formation of new cells. A person who is born before bomb testing and has adipocytes (or other cells) containing ^{14}C must have been generated these cells at later stages in life. Persons who are born when atmospheric ^{14}C content was high but their adipocyte cell DNA contains ^{14}C in amounts corresponding to the current lower atmospheric radioactive content have lost cells during the period from birth to current testing.

Estimation of the turnover of fat cell in humans

We adopted the above described ^{14}C method to determine age of living human fat cells[8]. Adipose tissue is a heterogenous organ. About 50% of the cell content is composed of non-adipocytes with a large capacity for cell division. The purity of the sample has to be > 95% of the total investigated cell population in order to be sure that contaminating cells do not contribute importantly to the measurements of radioactive DNA[7]. We developed a selection process that yielded at least 98% purity of the isolated fat cell preparation. By measuring ^{14}C content in the isolated DNA of these fat cells we detected significant amounts of radioactivity in all samples tested irrespective of age. In both lean and obese the mean fat cell age was about 10 years although the subjects were on average about 40 years old. This suggested that there is a marked generation of new fat cells per year and we found that about 10% of the cells are renewed every year. This means that after 10 year about half of all the adipocytes in the body are renewed whether you are obese or not.

Through mathematical modelling of ^{14}C in adipocyte DNA we determined the generation of new fat cells per year, the relative cell death of the fat cells and the age of fat cells[8]. Together these measures can be used to estimate adipocyte turnover in vivo. Mean fat cell age and death rate were not influenced by obesity. However, the generation rate of fat cell (new cells produced per year) was twice as high in obesity as compared to leanness, suggesting that obese

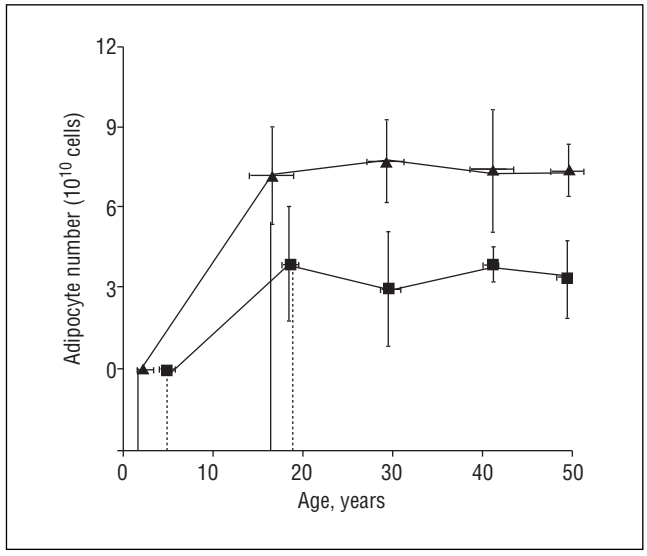

Figure 1 Turnover of fat cells in lean or obese humans overtime. Data adopted from reference 7.

subjects have an increased turnover rate of fat cells. Their bodies make twice as many new fat cells per year as the bodies of lean but at the same time twice as many of the old fat cells are dying per year in the total body of obese as compared to the lean.

We also investigated adipocyte turnover overtime[8] in a large cohort of children and adults[8]. The data are depicted in figure 1. When the same obese subjects was studied before and after marked weight reduction, the weight loss was accompanied by a marked decrease of fat cell volume but no change in fat cell number. Cross-sectional comparison of fat cell number between age bins, starting from early infancy up to late 70's revealed potentially important differences between lean and obese. In non obese subjects the generation of new fat cells starts at about 5 years of age, the production rate accelerates until about 19 years of age and thereafter the rate is constant onwards in life. In obese subjects the formation of new fat cells starts earlier, at about 2 years of age, accelerates until about 16 years (thus earlier than in lean) and thereafter the generation rate is constant throughout adult ages. Thus, the sensitive period in life for establishing adipocyte turnover is during infancy/ early adolescence and this period is prolonged in the obese. Once the adult age is reached the total number of fat cells in the body is constant in spite of ageing and weight loss. Recently we found that also weight loss due to cancer cachexia is accompanied by a decrease in fat cell volume although total fat cell number is not changed[9]. Together these data suggest that the total fat cell number in the body is under tight control due to the precise balance between the generation and dying of fat cells.

Clinical implications of adipogenesis

The finding that adipocyte turnover is very dynamic in adult man although the body keeps the total number of fat cells fixed in adulthood has potential implications for the

development of obesity and the ability to maintain a lower body weight after slimming. The prevalence of obesity is increasing markedly in most countries, even in less developed ones[10]. The mechanisms behind this "obesity epidemic" are not known but probably linked to changes in life style. Ongoing marked adipogenesis may also contribute since new small fat cells may be more biologically active than old large ones and have a prominent ability to rapidly fill up with lipids. Evidence for the latter theory has been generated by comparing the function and gene expression of small and large fat cells from the same subject[11,12]. The new fat cells generated during weight reduction may be more prone to fill up with lipids than pre-existing fat cells which would facilitate weight gain after stopping the obesity therapy. Indeed, post obese subjects have smaller fat cells than never obese subjects with the same body weight[13].

While the amount and the distribution of adipose tissue are associated with type 2 diabetes, metabolic syndrome and cardiovascular risk[14], the size of fat cell within the adipose tissue is also important[15]. Increased fat cell size correlates with serum insulin and triglyceride concentrations, with whole body insulin resistance and with increased risk of developing type 2 diabetes. The subjects with few large fat cells (adipose hypertrophy) are more at risk than those with the same degree of fat mass but have many small fat cells (adipose hyperplasia).

The mechanisms responsible for development of different from of adipose cellularity are now known, however, fat cell turnover may be involved. We are currently investigating adipocyte turnover in subjects with adipose hyperplasia or hypertrophy using our described ^{14}C method and are setting this in relation to the clinical profile in an investigation on about 1,000 subjects with available data on fat cell size and number.

Conclusions

There is marked generation of new fat cells in adult life. This is accelerated in subjects with juvenile onset obesity. However, the absolute turnover rate of fat cells is constant in adulthood irrespective of age and body weight and is not influenced by slimming. Adipogenesis could be an additional important factor (besides genetics, caloric intake and physical activity) in the development of obesity, for weight gain after stopping antiobesity therapies and for developing different forms of adipose cellularity (Fig. 2). Adipose hypertrophy (few large fat cells) is pernicious because it is associates with metabolic syndrome, cardiovascular risk and type 2 diabetes.

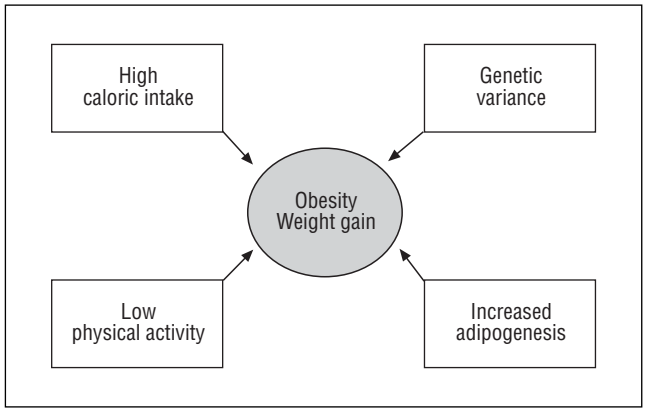

Figure 2 Factors of importance for accumulation of adipose tissue.

Conflict of interest

The author declares he has not any conflict of interest.

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