Adipose tissue and inflammation

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EDITORIAL

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What makes a good editorial?

Having written a few editorials over the years, focusing on the concept of what makes a good editorial is an interesting construct. There seem to be several subheadings that need to be recognised and either satisfied or challenged.

To begin with, the author(s) must be recognised as experts or rising stars in the field. An individual author's status will attract readers who in turn hopefully will look at the rest of the journal. In some journals (e.g. *IJCP*), the editor-in-chief writes personally and with a relatively free hand, but where comment is linked to an article within the journal or a specific topic of interest an 'expert opinion' is needed. Which leads to the second criterion – topicality.

A 'hot topic' will need to be not only written about swiftly but also published quickly. Online publication can easily be rapid but paper publication needs to be as adjacent as possible (it often is not). However, this will depend to some extent on the journal's publication frequency and thereby the lead-time to print. A journal fast-track print facility, as at *IJCP*, will need to be in place or here today editorials will be gone tomorrow without the expected recognition.

Controversial editorial comments can stimulate thought-provoking debate and where a subject is less than clearly defined a strong point of view can be refreshing. Inciting others to respond can shed light on equivocal management arenas. Challenging the conventional avoids bland matter of factness which in many editorial instances can be either boring, soporific or both.

Each journal has an audience and tailoring the editorial to the established readership is clearly important. The *IJCP* is a clinical journal, so an editorial on animal data or complex statistics will be inappropriate, yet targeted selectively welcomed elsewhere. Editorials as well as taking into account the clinical experience of the author(s) will also refer to clinical trials, systematic reviews and other valuable opinions but must do so in a way that stimulates interest rather than simply be a box-ticking factual exercise with no effective conclusion or recommendation.

There is no problem in my view in expressing strong critical opinions as long as they are factual rather than personal. If the opinion is not that of the author's institution it should be stated and the institution should be able to accommodate varying viewpoints – sadly and regrettably this is not always the case.

Finally, good editorials of whatever variety should be flagship articles for the journal publishing them.

At *IJCP* we usually invite authors but unsolicited editorials are welcome and all are subject to peer review. We work to 1000–1250 words and 20 references, but are flexible either way. We see editorials as informative, thought-provoking and potentially management-changing contributions and welcome them.

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Obesity is an established cardiovascular (CV) risk factor. In part this is attributable to an association with other CV risk factors, notably dyslipidaemia, hypertension and insulin resistance (IR) – the last being a central feature of the metabolic syndrome and a key predictor of the development of type 2 diabetes (T2D) and cardiovascular morbidity and mortality. Over the past decade it has become increasingly clear that pathological adipose tissue (AT) dysfunction is an early and central feature of

obesity and its sequelae (1). In this issue of the Journal, Weiss et al. report that a range of pro-inflammatory mediators, including matrix metalloproteinase-9, plasminogen activator inhibitor-1 (PAI-1) and interleukins (IL)-6 and -18, are upregulated in AT and that this increased expression is associated with CV risk (2).

In addition to its classic role as a store of body fat for release of lipids for oxidation by skeletal muscle during periods of fasting, AT functions as an endocrine and immune organ. In humans, the AT pool is comprised of two functionally distinct types of fat: white and brown. Both white adipose tissue (WAT) and brown adipose tissue (BAT) can be found in distinct areas or intermingled within certain depots. BAT is responsible for heat production through the process of non-shivering thermogenesis. WAT is the major AT in the body, which develops shortly after birth and gradually increases throughout life (3). The dispersion of WAT is mainly in intra-abdominal (visceral AT – omental, intestinal, perirenal) and subcutaneous (buttocks, thighs and abdomen) depots. WAT has a classical role in triglycerides storage, which provides a long-term fuel reservoir in mammals that can be used during meal intervals and also has a role in thermal and mechanical insulation. WAT is a heterogeneous tissue comprised of several cell types, including multi-potent adipocyte stem cells, pre-adipocytes, adipocytes, endothelial cells, histiocytes and macrophages. Adipose cells exhibit a degree of plasticity. It has been reported that multipotent adipocyte stem cells and pre-adipocytes can differentiate into macrophages (4,5), adipocytes can de-differentiate into pre-adipocytes and adipose stem cells (6,7), and adipose tissue macrophages (ATMs) can differentiate into pre-adipocytes (8). The physiological and pathophysiological importance of this cell plasticity remains to be fully elucidated. The major cell type within the WAT is the mature white adipocyte, which make up approximately 25–60% of the cellular content. White adipocytes are large, spherical cells (60–80 μm in diameter), characterised by a single lipid droplet and can store lipids up to 85% of the adipocyte cell volume (3).

Over the past decade it has become increasingly clear that pathological adipose tissue dysfunction is an early and central feature of obesity and its sequelae

The expansion of AT is the combined result of a size increase of pre-existing adipocytes (hypertrophy) and de novo adipocyte differentiation (hyperplasia) (1,3). Hypertrophic adipocyte growth is the initial step during positive caloric balance (1,3). In normal conditions, cell mass will increase to a maximum of ~0.7–0.8 μg lipids per cell, and thereafter there is a more rapid increase in fat cell numbers through hyperplastic growth. This type of response involves the recruitment, proliferation and differentiation of pre-adipocytes into mature adipocytes. However, during persistent positive caloric balance, such as is seen during sustained periods of weight gain, the AT has a lower capacity to recruit new adipocytes (1,3).

In obesity, there is a decrease in the differentiation of pre-adipocytes to mature adipocytes (9). Because of this disrupted production of new adipocytes, initial adipocyte hypertrophy continues in obese individuals (1,3). In effect, the AT contains greater numbers of large mature adipocytes and relatively fewer small newly differentiated adipocytes. When caloric intake exceeds caloric expenditure, the positive caloric balance and energy storage within AT often results in adipocyte hypertrophy and visceral fat accumulation. There is accumulating evidence that hypertrophic adipocytes are independently associated with IR (10,11). Hypertrophic adipocytes exhibit a reduced capability to retain fatty acids (FA), resulting in an 'overspill' of lipids into the circulation. In defence, peripheral tissues including the liver and skeletal muscle, attempt to dispose of these free FAs (FFA) through induced-FA oxidation. However, once energy entering these tissues exceeds the oxidative and storage capacity, excess lipids instead follow an alternative non-oxidative pathway. As a consequence of this alternate pathway, toxic reactive lipid species are synthesised and they begin to accumulate within peripheral tissues. These affects lead to lipotoxicity, a process that promotes IR (1).

Fat distribution exhibits gender differences with premenopausal women demonstrating generalised lipid distribution, in contrast to men who tend to accumulate fat centrally. There are also gender differences in the ratio of visceral to subcutaneous fat mass – in women, visceral fat mass represents approximately 50% of subcutaneous fat mass, while for men this rises to 98%. It has been reported that increases in visceral omental (android/central obesity) AT correlates more strongly with IR and cardiovascular disease (CVD) than increases in abdominal subcutaneous AT (gynoid obesity). However, it is important to consider that the amount of visceral fat exhibits an allometric relationship with total body fat content, such that obesity-associated changes in visceral fat mass reflect the initial ratio of visceral fat to total fat mass, as well as the changes in total fat mass. Thus, weight gain or loss is associated with changes in both visceral and subcutaneous fat mass. It has been speculated that subcutaneous AT acts as a sink to contain lipotoxic products and, thus, prevent these from entering the circulation and having detrimental effects on body organs such as the liver and muscle. This role for subcutaneous AT in preventing ectopic lipid deposition has been lent support by the recent identification of a locus near the gene for insulin receptor substrate 1 (*IRS1*) as being

associated with a lower body fat percentage in men, specifically with less subcutaneous than visceral fat (12). Significantly, this locus, which results in reduced subcutaneous AT expression of *IRS 1*, has also been associated with detrimental metabolic traits including IR, dylipidaemia and reduced adiponectin levels, as well as with an increased risk of T2D and coronary artery disease (13,14), leading to speculation that impairment in subcutaneous AT expansion may lead, ultimately, to the disruption of insulin signalling in the liver, whole body IR and dyslipidaemia.

Evidence has been provided that infiltration of AT by adipokine-dependent extravasated peripheral blood monocytes increases during obesity and that these cells are central to the inflammatory events that are characteristic of obese AT (1). Adipocyte size is a strong, direct predictor of ATM recruitment and accumulation (15). During AT expansion, enlarged, hypertrophic adipocytes are known to outstrip the local oxygen supply, causing AT hypoxia (16). Thereafter, such hypoxic conditions have been noted to induce necrosis-like adipocyte cell death. Because of the phagocytic actions of macrophages, there is enhanced infiltration to this area in response to cell death. Macrophages have been detected in the subcutaneous and visceral AT of obese patients, in which they surround the dead adipocyte in a crown-like arrangement (15). ATMs represent a class of pro-inflammatory peripheral monocytes that infiltrate the AT and are responsible for potentiating the chronic inflammatory processes of obesity (1). There is also evidence that ATMs prevent pre-adipocyte differentiation and exert inhibitory effects on adipocyte insulin-mediated glucose transport (17,18). Both subcutaneous and visceral ATM number correlate with clinical parameters of obesity and its co-morbidities (19), moreover, the pro-inflammatory activation state of ATMs have also been reported to correlate with IR (20).

Dysfunctional AT exhibits increased production of pro-inflammatory mediators, including adipokines/cytokines (e.g. tumour necrosis factor-α, IL-6 and -18, PAI-1), acute phase proteins (e.g. serum amyloid A) and chemoattractants (e.g. monocyte chemoattractant protein-1) (1). Dysfunctional AT also exhibits reduced production of anti-inflammatory molecules, most significantly the insulin-sensitising adipokine adiponectin. In this manner, obese AT contributes to the chronic inflammatory processes that underlie the development of metabolic syndrome, diabetes and CVD. It is important to note that AT is heterogeneous with respect to mediator profile; mediator expression levels have been reported to differ significantly according to WAT anatomical site. Indeed, gene expression differences between subcutaneous and visceral WAT have been used to explain the link between central obesity and cardiometabolic outcomes (21,22). Crucially, however, evidence that inflammatory mediator upregulation precedes hyperinsulinaemia and overt hyperglycaemia indicates that adipose inflammation is centrally involved in the metabolic complications of obesity. Within dysfunctional AT inflammatory mediators are produced predominantly by adipocytes and ATMs, with the relative contribution of each cell type differing for each mediator (21,22). Adiponectin is produced largely by adipocytes, such that its reduced production in obesity is reflective of impaired adipocyte function. With respect to adipose tissue-derived factors and cardiometabolic risk, adiponectin is almost certainly the most informative. Adiponectin levels are inversely correlated with IR and risk of T2D. In terms of specific risk biomarkers for CVD and diabetes, a recent report examining the contribution of different biological pathways to the development of T2D concluded that adiponectin was the most important contributor, explaining one-third of the risk (23).

While vitamin D deficiency/insufficiency (hypovitaminosis D) has been reported in numerous recent studies to be associated with obesity, dyslipidaemia, hypertension, CVD and T2D, a recent meta-analysis has reported that there is insufficient evidence to conclude that an inverse association exists between vitamin D levels and a range of cardiometabolic outcomes (24). Obesity has been reported to be characterised by a deficiency of both 25 hydroxyvitamin D (25-OH D) and the vitamin D receptor ligand, 1, 25 dihydroxyvitamin D (1, 25-OH_2 D) (25,26). It has been suggested that vitamin D deficiency in obesity is simply a bystander effect due to increased sequestration and storage of 25-OH D in excess AT (27). However, it has also been reported that in obesity, 25-OH D levels are negatively correlated with surrogate markers of both IR and β cell function (28), and positively associated with adiponectin levels (29). A recent analysis of the U.S. National Health and Nutrition Examination survey has indicated that lower serum 25-OH D levels are associated with prediabetes – a stage of the hyperglycaemia/T2D continuum where individuals have a heightened risk of developing diabetes and where, crucially, prevention strategies have been effective in delaying or preventing the onset of T2D (30). Further, vitamin D intervention trials, while limited and not in uniform agreement, have provided positive results regarding the impact of vitamin D supplementation on glucose regulation (31–33). Given the obvious ambiguity in determining both an association between hypovita-

minosis D and cardiometabolic disease, and also the mechanism(s) by which vitamin D might effect cardioprotection, robust, well designed vitamin D intervention trials are clearly required to determine whether, and how, this hormone may be involved in the development of CVD and T2D.

In conclusion, storage of excess calorific intake in body fat results in enlargement of adipocytes and their consequent hypertrophy. Fat storage via recruitment, proliferation and differentiation of adipocytes is impaired, resulting in further adipocyte hypertrophy and leading, ultimately, to the generation of dysfunctional AT characterised by increased release of FFA, macrophage infiltration and inflammation, dysfunctional interactions with other body organ systems and pathogenic fat distribution. Given that adipose dysfunction is a significant contributor to the chronic inflammatory processes of obesity, preceding hyperinsulinaemia and overt hyperglycaemia and, thus, is an early and central event in the development of T2D and CVD, it could be argued that non-pharmacological and pharmacological interventions with the ability to ameliorate this dysfunction (34) would have the greatest impact if directed at obese, non-/prediabetic individuals (35,36), in addition to those with established CV risk factors or T2D.

Disclosures

None.

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