Obesity, which is defined by an excess of body fat associated with increased health risk, generally diagnosed on the basis of a body mass index (BMI) greater than 30 kg/m² has reached epidemic proportions in many countries. According to a recently published report 1.46 billion adults were overweight, and 502 million adults were obese in 2008 worldwide (1). Through its association with chronic diseases such as insulin resistance, type 2 diabetes, hypertension and coronary heart disease, obesity strongly impacts on cardiovascular health (2, 3) and cardiovascular disease (CVD) is still the main cause of death in men and women globally (4). Notably, among CVD risk factors, only obesity and current smoking has been independently associated with the risk for venous thromboembolism (5).

Although it is therefore well established that obesity is a health hazard, additional evidence indicates that obesity may exist without the expected CVD risk factors (6, 7). On the other hand, metabolically unhealthy non-obese subjects are at increased risk for CVD and all-cause deaths. Thus one of the key questions to be answered is how to identify obese patients with a considerable risk for atherothrombotic disease. The present issue of the journal provides an update on some new aspects on the relation between obesity and CVD both at physiopathological and therapeutic levels.

In this Theme Issue of Thrombosis and Haemostasis focused on “Obesity and vascular disease: From bench to bedside”, Scroyen et al. review experimental in vitro and in vivo murine models of obesity and discuss their value in understanding the mechanisms contributing to obesity (8). Although murine adipocyte cell lines and freshly isolated preadipocytes are currently widely used in obesity-related research, several concerns are warranted. Development of obesity in rodents may depend on several genetic and environmental factors different from the situation in humans. Among the most recently identified factors, modification of the microbiota deserves to be mentioned. A corollary to this is the potential for manipulation of the gut microbiota in the prevention and management of obesity and associated metabolic disorders (9). Also, differences between human and mouse obesity fat distribution are obvious. Indeed the dramatic gender-related differences in fat distribution and mass that are seen in humans are not found in mice. In addition in contrast to mice only discrete amounts of metabolically active brown adipocytes exist in adult humans (10). This may be another reason for mouse-human metabolic differences.

Obesity is characterised by a chronic state of low-grade inflammation, and adipose tissue inflammation has been linked to obesity-related metabolic complications, such as the development of insulin resistance (11). Rega-Kaun et al. indicate that an integrative approach to the understanding of obesity and its complications involves feedback from autocrine and paracrine effectors secreted by a dysfunctional adipose tissue mainly characterised by an inflammatory status mediated not only by adipocytes but also by immune cells such as macrophages and lymphocytes present in adipose tissue (12). Numerous adipokines, chemokines, and cytokines that are secreted by large adipocytes and the stromal vascular fraction feed back to other organ systems and impact on the development of CVD. In addition to elevated leptin, decreased adiponectin and increased PAI-1 levels, omentin appears to be an interesting marker of CVD in obesity. Osteopontin and pigment epithelium-derived factor are also expressed in adipose tissue and represent new targets whose role in CVD awaits further characterisation.

There is now precise evidence from several computed tomography and magnetic resonance imaging studies that excess visceral/ectopic adiposity and organ fat content e.g. in liver, heart, muscle or pancreas are key drivers of cardiometabolic risk associated with a given level of total body fat. Morelli et al. describe new relevant findings linking ectopic fat to cardiometabolic disease (13). Growing evidence suggests that obese individuals who are metabolically healthy have lower levels of liver fat and visceral adipose tissue than obese and metabolically unhealthy individuals. Importantly visceral fat accumulation also in non-obese people exhibiting metabolic complications. An increase in ectopic fat mass may correspond to the failure of subcutaneous fat to handle lipid overflow due to insulin resistance and due to limitations in blood supply that may impair the lipid buffering capacity of the large subcutaneous adipocytes. Dysfunctional ectopic fat, specifically epicardial fat and fat inside the myocardium, has been directly implicated in increased cardiovascular risk in affected individuals. However, other ectopic fat depots may indirectly contribute to this risk through dyslipidaemia, inflammation, oxidative stress and secretion of adipokines. Ectopic fat may therefore become a new and promising target for therapeutical intervention.

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Received: August 20, 2013
Accepted: August 20, 2013
Prepublished online: September 12, 2013
doi:10.1160/TH13-08-0685
Adipose tissue and its vasculature are constantly remodelled during periods of weight gain or weight loss. Several adipokines stimulate angiogenesis and many key factors of angiogenesis are strongly expressed by adipose tissue. It is suggested that the vascular network plays a role in angiogenesis although the exact relation is still unclear. In their review Lemoine et al. present a link between angiogenesis, obesity and insulin resistance in which hypoxia resulting from inadequate angiogenesis leads to inflammation, fibrosis and ultimately to insulin resistance (14). Interestingly inhibition of angiogenesis has been shown to prevent obesity in mice. Blockade of VEGF-R2 restricts adipose tissue expansion and inactivation of PIGF in mice leads to impaired adipose tissue development. Results obtained with inducers of vessels apoptosis are promising but this strategy needs to consider an unwanted growth of ectopic fat in response to blocking the development of subcutaneous adipose tissue.

Accumulation of ectopic fat is accompanied by important changes in the haemostatic balance, which lead to a prothrombotic state. Morange and Alessi in their review depict platelet and endothelial dysfunction and the resulting changes in coagulation and fibrinolysis that accompany visceral obesity (15). Specific mechanisms involved in these changes include inflammation, insulin resistance, oxidative stress and dyslipidaemia. But also ectopic fat contributes to a procoagulant and hypofibrinolytic state seen in obesity. Overall these changes support the notion that visceral obesity rather than BMI per se is associated with cardiovascular morbidity and mortality. Given the evidence for an association between central obesity and changes in haemostasis most of the current literature points towards a link between visceral fat and venous thrombosis.

In addition to a prothrombotic state, obese patients exhibit a poor response to antithrombotic therapy. Badimon et al. reviewed the particularities of antithrombotic treatment in obesity. Obesity may potentially interfere with the absorption, distribution and metabolism of drugs (16). Platelets from obese individual retain higher residual platelet function despite aspirin or thienopyridines treatment. Obese patients exhibit a higher susceptibility to dyspnea as a side effect accompanying antithrombotic therapy with ticagrelor. In general physiological alterations and a lower response to some antiplatelet agents and anticoagulants seen in obese individuals indicate that dosage regimes need to be specifically adjusted for these patients. With heparin close monitoring of the therapeutic effects allows adjusting the dose according to the response of the individual patient. The fixed dosing schedule with recent new anticoagulants raises the question of appropriate dosing in the obese population. Yet, lifestyle modifications appear a complementary beneficial strategy.

In her contribution, Van Baak describes how nutritional intervention may reduce obesity and ectopic fat (17). Diets lower in total fat were associated with lower relative body weight. Fatty acid composition of the diet may have an impact on body fat distribution patterns with moderation of the intake of saturated fatty acid being the most effective measure. Limiting calorically sweetened beverage consumption will lower fat mass and ectopic fat. Thus quantitative as well as qualitative diet modification may have an impact in facilitating the prevention of unhealthy fat accumulation.

In summary the reviews collected in this Theme Issue follow a bench-to-bedside approach to provide an overview on the current state of research in the area of obesity and its impact on CVD by discussing murine models of obesity, the role of adipose tissue as a source of bioactive molecules, the impact of ectopic fat on cardiovascular disease, a link between angiogenesis and obesity, the connection of thrombosis, obesity and the metabolic syndrome, new aspects of antithrombotic therapy in obese patients and the role of lifestyle modification in the prevention of obesity. Given the increasing numbers of obese individuals worldwide further research in the area seems highly warranted in order to identify new therapeutic targets for treatment of the disease and – even more importantly – to develop efficient strategies for its prevention.

Conflicts of interest
None declared.

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