Obesity and vascular risk

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Summary
Obesity is a common disorder and a known risk factor for vascular thrombotic complications. Development of obesity is associated with extensive modifications in adipose tissue involving adipogenesis, angiogenesis and extracellular matrix proteolysis. Studies using a nutritionally induced obesity model in transgenic mice support a role of the fibrinolytic (plasminogen/plasmin) and matrix metalloproteinase (MMP) systems in these processes. Venous or arterial thrombosis models in obese mice confirm a prothrombotic risk associated with obesity.

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Obesity increases the risk of multiple conditions, including cardiovascular and cerebrovascular disease (7). The MEGA study recently confirmed that overweight (BMI ≥ 25 kg/m²) and obesity (BMI ≥ 30 kg/m²) increase the risk of venous thrombosis by 1.7-fold and 2.4-fold, respectively (20). In postmenopausal women, overweight or obesity are associated with odds ratio for venous thromboembolism of 2.5 or 3.9 (1).

Development of obesity is associated with extensive modifications in adipose tissue involving adipogenesis, angiogenesis and proteolysis of the extracellular matrix (ECM) (3). Proteolytic systems, such as the plasminogen/plasmin (fibrinolytic) and matrix metalloproteinase (MMP) systems, contribute to tissue remodeling by degradation of the ECM and basement membrane components or by activation of latent growth factors.

The fibrinolytic system

The fibrinolytic system comprises an inactive proenzyme, plasminogen, that can be converted to the active enzyme, plasmin, that degrades fibrin into soluble fibrin degradation products (11). Two immunologically distinct plasminogen activators have been identified: ● tissue-type plasminogen activator (t-PA), ● urokinase-type plasminogen activator (u-PA).

Inhibition of the fibrinolytic system may occur either at the level of plasmin by α2-antiplasmin, or at the level of the plasminogen activators, by plasminogen activator inhibitors (PAI-1 and PAI-2) (11).

Role of fibrinolytic components in adipose tissue development

Nutritionally induced obesity models in transgenic mice have been used to study the role of fibrinolytic system components in the development of obesity. t-PA deficient mice, kept on high fat diet, had higher body weight and adipose tissue mass than wild-type controls (17). Deficiency in u-PA, in contrast, had no effect in this model of nutritionally induced obesity (17). Mice deficient in plasminogen, the substrate for both plasminogen activators, showed reduced fat accumulation associated with reduced differentiation of stromal cells (6). Deficiency of α2-antiplasmin had no significant effect on adipose tissue development in mice (14). Direct comparison of studies may be hampered by differences in genetic background of the mice used and in composition or timing of the diet.

The role of PAI-1 in adipose tissue development at present still remains controversial (reviewed in 12). Recently, this was reinvestigated with the use of PAI-1 deficient mice and true littermate wild-type controls in an identical genetic background (13). When kept on high fat diet for 15 weeks, there was no difference between both genotypes in body weight or in weight of the subcutaneous (SC) adipose tissue, whereas the gonadal (GON) fat mass was larger in PAI-1 deficient mice. In transgenic mice with adipose tissue specific overexpression of murine PAI-1 reduced fibrinolytic activity resulted in a reduction of nutritionally induced obesity (9). Significant adipocyte hypotrophy was observed in the SC adipose tissue of PAI-1 transgenic mice, and the ratio of stroma cells versus adipocytes was significantly lower both in SC and GON adipose tissue of transgenic as compared with wild-type mice. Analysis of blood vessels did not reveal significant differences. Overexpression of PAI-1 thus seems to modify the cellularity of adipose tissue, however without significantly affecting angiogenesis.

Overall, the effect of PAI-1 on adipogenesis appears to be concentration-dependent. Preliminary data indicated that pharmacological inhibition of PAI-1 in mice fed a high fat diet, resulted in reduced body weight and a small improvement in metabolic parameters; reviewed in (2).

The MMP system

The matrix metalloproteinase (MMP) system consists of a family of over 25 neutral endopeptidases that are collectively able to cleave all of the ECM components as well as several non-ECM proteins, such as adhesion molecules, cytokines, protease inhibitors and other (pro) MMPs. Generally, MMPs are expressed at low levels but are rapidly induced at times of active tissue remodelling. Most MMPs are secreted as inactive proenzymes and require proteolytic processing to become active. MMP activity is modulated through interactions with tissue inhibitors of MMPs (TIMPs). Four TIMPs have been characterized that are able to inhibit the activities of all known MMPs. Consequently, the net MMP activity in tissues is locally determined by the balance between the levels of activated MMPs and TIMPs (5).
the expression of MMPs and TIMPs was monitored in adipose tissues of lean and obese mice (15). This revealed
- upregulation with obesity of mRNA levels of some MMPs (MMP-3, -11, -12, -13, -14) and
- downregulation of others (MMP-7, -9, -16, -24).

Inactivation of the stromelysin-1 (MMP-3) gene in mice resulted in enhanced development of adipose tissue when fed a high fat diet, characterized by hypertrophic adipocytes in the SC and GON fat pads (16). A higher blood vessel density was observed in the adipose tissue of MMP-3 deficient mice, suggesting that MMP-3 affects adipose tissue-related angiogenesis. Stromelysin-3 (MMP-11) deficiency also promoted adipose tissue development and resulted in adipocyte hypertrophy (8). We have recently shown that MMP-2 deficient mice when kept on a high fat diet, but not MMP-9 deficient mice, show significantly reduced obesity associated with adipocyte hypertrophy, without effect on angiogenesis (22).

TIMP-1 deficient mice on a high fat diet gained less weight than their wild-type counterparts and developed less adipose tissue (10). To further substantiate a role of TIMP-1 in nutritionally induced obesity, the effect of TIMP-1 overexpression by adenoviral gene transfer in mice was studied on adipogenesis and adipose tissue development (4). Long-term expression of highly elevated levels of human TIMP-1 was associated with reduced MMP activity in plasma, as well as in adipose tissue. There was no significant effect on body weight or fat pad mass when the mice were kept on high fat diet. The extent of de novo fat pad formation in NUDE mice following injection of adipocytes was also not affected by local or systemic overexpression of human TIMP-1 (21). It is conceivable that physiologic TIMP-1 concentrations in mice are sufficient to promote adipogenesis and adipose tissue development, whereas overexpression has no further effect, and deficiency results in impairment.

Administration to wild-type mice kept on HFD of broad-spectrum MMP inhibitors or of relatively gelatinase specific inhibitors resulted in moderate to significant reduction of adipose tissue weight, supporting a functional role of MMPs; reviewed in (2).

Obesity and thrombosis

Analysis of the plasma coagulation profile of lean and obese C57Bl/6 mice revealed significantly higher levels of PAI-1, FVIII activity, antithrombin III antigen and combined FII/VII/XI activity for the obese animals. Fibrinogen levels and FV activity were not different, whereas thrombin-antithrombin III complex levels were enhanced in obese mice. Using a FeCl3 induced femoral arterial thrombosis model in lean and obese Swiss mice, the obese mice showed a significantly shorter occlusion time and lower total blood flow. A significant negative correlation was observed between body weight and both occlusion time and blood flow (19).

Photochemical induction of middle cerebral arterial occlusion resulted in significantly shorter occlusion times in nutritionally induced obese mice than in lean wild-type (C57Bl/6) mice, whereas the infant size was significantly larger and intracranial haemorrhage enhanced. Similar observations were made in genetically obese ob/ob mice, as compared to lean wild-type littermates (18). In both models, obesity was associated with markedly elevated circulating PAI-1 levels, probably originating from the fat tissue. These animal models support experimentally a correlation between obesity and prothrombotic tendency.

References