The Important Roles of Matrix Metalloproteinases in the Pathophysiology of Obesity

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Obesity involves the growth of adipose tissue cells (adipocytes and preadipocytes), as well as microvascular endothelial cells. Matrix metalloproteinases (MMPs) are relevant enzymes for the modulation of extracellular matrix (ECM) and adipocyte and preadipocytes differentiation. They are elevated in obese patients, generating abnormal ECM metabolism [1]. This article proposes a thorough study of literature with focus on the important roles of matrix metalloproteinases in the pathophysiology of obesity. The article represents a narrative review based on an English-language PubMed research of the medical literature regarding important aspects of the proposed aim. MMP-2 activity was significantly higher than MMP-9, both activities were detectable. MMP-9 was strongly correlated with body weight parameters before surgery, as well as after significant body weight reduction as a result of bariatric surgery. Concerning MMP-2 and MMP-9 they are also involved in the turnover of basement membranes both those of adipose tissue and endothelial. MMP-9 levels were moderately correlated with HDL cholesterol levels. Taken together, the present data suggest that changes in ECM through MMP-mediated degradation might play a critical role in the adipocyte differentiation process. These findings are detected both in clinical trials and in laboratory animal experiments. It is then tempting to speculate that the adipocyte-derived MMPs might represent a new pharmacological target for the inhibition of adipose tissue growth by inhibiting adipose differentiation as well as angiogenic process.

Keywords: matrix metalloproteinases, bariatric surgery, adipocyte, preadipocytes

Experimental part

Materials and methods

This article proposes a thorough study of literature with focus on the important roles of matrix metalloproteinases (MMPs) in the pathophysiology of obesity. The article represents an ongoing experimental study and a narrative research review based on a PubMed search of the medical literature regarding important aspects of the proposed aim. There were selected only the relevant studies for the hypothesis.

The ongoing study comprises 40 obese wistar rats divided into 4 groups of 10 rats. The first group is the control group, the second group is the gastric bypass group, the third received only the subcutaneous injection daily (sulodexide 10u / kg), and the 4th received the injected substance and suffered gastric by-pass surgery. Rats were induced obesity by a hypercaloric and hyperlipidic diet according to literature data, reaching a specific weight for obese rats. The stages of the study are still under way, but so far they support the data collected from the literature that are reviewed in the results chapter and subsequent discussions. Sulodexide is a highly purified mixture of glycosaminoglycans composed of low molecular weight heparin (80%) and dermatan sulfate (20%). Sulodexide exhibits marked antithrombotic action at both arterial and venous levels - factor X activated. Sulodexides normalize the altered parameters of blood viscosity, this action is manifested especially by decreasing plasma fibrinogen concentrations. Attention is especially on the effects of preventing and stopping complications of diabetes, the peritoneal anti-inflammatory effect and the direct action on metalloproteinases - MMP-9, TIMP-1. In this regard, we are doing the present review to have a much clearer picture of the effects of the matrix metalloproteinases.

Results and discussions

The obesity pathophysiology is characterized by systemic inflammation, macrophages infiltration of adipose tissue and also a remodeling of the ECM regulated by MMPs. The infiltration of macrophages is a characteristic sign of...
obesity-related adipose tissue inflammation [3]. Macrophages infiltration is also very important in the regulation of ECM turnover and fibrogenesis involving, of course, several MMPs.[3]

The same changes have been reported in fatty liver macrophage in obesity models.[8] There is still needed some data to establish a correlation between inflammation and MMP expression in adipose and liver tissue. For an organ to develop areas of fibrosis is necessarily be an area of inflammation before and the imbalance of ECM production (that means fibrogenesis) versus ECM degradation (that means fibrolysis) [9].

It was demonstrated that a diet containing 60% of calories from fat can cause a high levels of fat index (as an index of obesity) and so can induce obesity. Also, it induces insulin resistance and hepatic steatosis over time, diseases directly associated with obesity.[7, 10]. The development of diet-induced obesity was correlated with high expression of MMPs in adipose tissue. The relevant ones are: MMP-2, MMP-3, MMP-8, MMP-12, MMP-13, TIMP-1, TIMP-2, ADAM-17, which emphasizes the idea reported in the literature. The most robust finding, in the majority of studies, was an increase in gene expression for MMP-3, MMP-8, MMP-12, MMP13 and TIMP-1 [12].

To remove the excess ECM and allow adipocyte hypertrophy, MMPs play a central part in the control of adipogenesis through the proteolytic activities that takes place during fat mass enlargement.

A 2012 meta-analysis showed that there is a statistical significant decrease in CRP and IL-6 levels after bariatric surgery. These cytokines are very important in the pathogenesis of some important diseases such as coronary heart disease and diabetes mellitus [6, 11].

MMPs are also involved in glucose homeostasis: Derosa et al. found in their studies an increased plasma levels of MMP-2, MMP-9, TIMP-1 and TIMP-2 in diabetic subjects, which reflect extracellular matrix metabolism disturbance in diabetes [13]. The hypothesis was sustained also by Boden et al. They reported hyperinsulinemic status in an euglycemic-hyperinsulinemic clamp and an increases MMP-2, MMP-9 and membrane MMP-1 level activities in aortic wall endotelium [2, 14].

**MMP in other related diseases**

It’s well known that obesity is an independent risk factor for many comorbidities like diabetes, hypertension, atherosclerosis and vascular and cardiac dysfunctions [15]. Increased energy intake and a decreased energy consumption represents the substrate for the adipocytes and this mechanism is leading to hypertrophy [2].

Atherosclerosis involves activity of extracellular MMP-2 and MMP-9, E-selectin and adiponectin. The MMPs are involved in remodeling of extracellular matrix and also of basal membranes. The imbalance between MMPs and TIMPs (MMPs inhibitors) [16] and the α-2-macroglobulin determine proteolysis and endothelial damage or the excess accumulation of matrix constituents [17]. MMPs are very important in the modulation of adipogenesis, atherosclerotic process, [4] in remodeling of the blood vessels endothelium and cardiac muscle [18-20].

According to some authors, adiponectin is negatively correlated with BMI, visceral fat and the body weight [21]. In contrast, other studies doesn’t confirm this correlation to other hormones originating from the adipose tissue [22-25]. In clinical practice, hypoadiponectinemia is considered to be a positive predictor of lipid disorders, diabetes (type II), hypertension and nonalcoholic fatty liver disease [7].

In some studies, there are some correlations between BMI and E-selectin levels on one hand and MMP-9 levels on the other hand. Strong correlation was also found between MMP-2 and MMP-9. There is also a relationship between MMP-2 and adiponectin levels. On the other hand, MMP-9 levels were moderately correlated with HDL cholesterol levels [7].

Adipocyte hypertrophy and hyperplasia have been intensely studied. The pathophysiologic mechanisms of these processes are not yet completely understood. There are few data available concerning the regulation of angiogenic processes and the mädification of the ECM during obesity increasing process in time. Adipocytes have important metabolic activities and they are able to produce some factors such as cytokines and growth factors, which play important roles in adipose tissue remodeling by paracrine regulation [26]. On the other hand, adipocytes also secrete proangiogenic factors, such as vascular endothelial growth factor (VEGF), tumor necrosis factor-α, monobutyrin, and leptin [7]. Some ECM components are both synthesized and degraded during the process of adipocyte differentiation [27, 28].

The confirmation of the adipocyte origin of MMPs was done on freshly isolated mature adipocytes [8]. RT-PCR analysis with specific primers for MMP-9 and MMP-2 revealed the presence of the two transcripts in human adipocytes, although the genetic expression of MMP-9 was lower than MMP-2 and had high variations. There is data that demonstrate, in human adipose tissue, that the activity of MMP-2 is much higher than that of MMP-9. Moreover, both pro-MMP-2 and MMP-2 were found in the same conditions. MMP-9 had a moderate increase in the first 7 days, with the higher level in day 7, and decreased after that [8].

Mirrored those mentioned the inhibition of MMP-2 and MMP-9 modify adipocyte differentiation. Preadipocytes may be the element that leads to the correlation between the differentiation of adipocytes and MMPs. To determine whether MMP activity released by adipocytes play an important role in the differentiation process, preadipocytes were treated with increasing concentrations of MMP inhibitors, like batimastat (0.5 - 10 mmol/L), and with captoiol (10 -1,000 mmol/L) in the presence of adipogenic medium [8].

The first evidence that human adipose tissue (adipocytes and preadipocytes) produce MMP-9 and MMP-2 provided by Anne Bouloumie et al followed by further analysis of the adipocyte-derived secretion of MMPs performed on the murine preadipocyte, demonstrates that MMP-2 and MMP-9 are synthetised and released during adipocyte differentiation. Indeed, although the MMP-2 activity was significantly higher than that of MMP-9, both activities were detectable. These results clearly show that MMPs play a key role in adipocyte differentiation[8].

Despite what was said earlier adipocyte showed very high individual variations, suggesting that adipocyte-derived MMP synthesis, secretion, and activity can be under the control of still some unknown modulating factors.

Taken together, the present data suggest that ECM changes through MMP-mediated degradation play a critical role in the differentiation of adipose tissue. Since there is some data that described that angiogenesis stimulated by adipocyte conditioned medium was inhibited by TIMP [27], it is tempting to speculate that MMPs can represent a new and very interesting therapeutic target to estimate adipose tissue modifications by reducing adipose differentiation, on the one hand and inhibiting the angiogenic processes, on the other.
A number of studies demonstrated that MMP-9 levels were higher in patients with obesity (BMI values) and metabolic syndrome as compared to patients with normal body weight and no metabolic disorders [29]. There are data showing the relationship between body weight parameters and MMP-9 in patients with morbid obesity before and after bariatric surgery and [29] significant body weight loss.

The benefits of bariatric surgery are not just of biological nature, but also aim the improvement of quality of life. There are studies pending for publication [12] that demonstrate most of the patients that undergone bariatric surgery have improved both sports performance and frequency and have improved sexual status ($p < 0.05$). Also there was an improvement of the libido and quality of intercourse in 44% of the included patients [12]. The minimally invasive approach of bariatric surgery allows a quick reinsertion of the individual in the daily activities. Bariatric surgery should be understood in all the positive changes that it generates in everyday life.

**MMPs in diabetes**

In addition to body weight control, bariatric surgery can significantly improve glycemic control in obese patients with type II diabetes [30, 31]; therefore, it is also referred to as metabolic surgery. Furthermore, the effect on the body weight and type II diabetes depends on the type of bariatric surgery [32, 33], but the detailed mechanisms of these effects remain unknown.

Many biological mechanisms are suspected to play important roles in the pathophysiology of diabetes. For example: fetuin-A is a hepatic secretory protein that binds the insulin receptor and inhibits insulin signaling by inducing insulin resistance in vitro [34-36]. MMP-7 is another marker of diabetes that can digest structural proteins of the ECM. It plays essential roles also in cancer, innate immunity, and inflammatory disorders (such as scleroderma). Elevated serum MMP-7 levels have also been found in patients with type II diabetes and diabetic renal disease [37]. However, the exact mechanism remains quite obscure.

The preoperative serum MMP-7 level was associated with age, indices of central obesity, and other metabolic disorders (obesity-related), as was showed in several studies. Elevated serum MMP-7 levels are related to cardiovascular disease, type II diabetes, intra-abdominal fat, and hepatic steatosis [34-36].

Diabetes is making the difference regarding fetuin-A and MMP-7 levels in obese patients. Bariatric surgery (RYGB, MGB, and SG) decreased the circulating fetuin-A levels at one year after surgery, also reducing glycemic levels and improved QoL and improved sexual life or increased frequency of making sport. The minimally invasive approach of bariatric surgery allows a quick reinsertion of the individual in the daily activities. Bariatric surgery should be understood in all the positive changes that it generates in everyday life.

MMPs can also regulate in a negative way the angiogenesis by producing anti-angiogenic peptides. Angiostatin is an N-terminal breakdown product of plasminogen that can be generated by MMP-2, MMP-3, MMP-7, MMP-9, and MMP-12.

However, the importance of MMPs in down-modulating angiogenesis is unclear, whereas they are clearly important positive regulators of angiogenesis [38].

**MMPs in Cancer**

MMPs are present in large quantities and are activated more often around malignant cancers than in normal, benign, or premalignant tissues, with the highest expression taking place in some areas of active invasion at the tumor-stroma interface [39]. Significant positive correlations have been found between MMP expression and various indicators of a poor prognosis in almost all types of cancer. Can be considered that increased MMP levels represent an independent predictor factor of shortened disease-free and also as an overall survival factor [39].

It was demonstrated that benign cells acquire malignant properties when MMP activity is increased or TIMP activity diminished. By reducing the MMP levels or by inhibiting their activity the malignant cells can become less aggressive. There are several MMPs implicated as antagonists angiogenesis, tumor invasion and tumor metastasis – MMP-1, MMP-2, MMP-3, MMP-9, and MMP-14 [39]. If the ECM is not degraded the endothelial cells are not able to penetrate it, so if the malignant cells does not inhibit or degrade the ECM they couldn't spread above it. However, recent data indicate that MMPs do more to influence cancer than just remove the physical barriers, there are some MMPs that can promote early cancer development, and MMP-3 can also promote late epithelial-to-mesenchymal phenotypic changes that are associated with more aggressive malignant behavior. These data suggest that MMPs can contribute to all stages of cancer evolution, both early and late. Some MMPs may defy cancer progression, and others may not participate in cancer, but undoubtedly play normal physiologic roles. These possibilities must be considered and the mechanisms underlying the influence of MMPs in cancer must be understood in terms of therapeutic agents in order to optimize their efficacy and minimize their toxicity [38,39]. The proteolytic cleavage of the ECM plays a key role in the malignant development.

**Conclusions**

It is tempting to speculate that MMPs can represent a new and very interesting therapeutic target to estimate adipose tissue modifications by reducing adipose differentiation, on the one hand and inhibiting the angiogenic processes, on the other.

Improving quality of life is directly related with the number of lost kilograms, with % EBWL and so with the postoperative BMI. Also, there is a correlation between improved QoL and improved sexual life or increased frequency of making sport. The minimally invasive approach of bariatric surgery allows a quick reinsertion of the individual in the daily activities. Bariatric surgery should be understood in all the positive changes that it generates in everyday life.

**References**


Manuscript received: 3.02.2017