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Pathophysiology of metalloproteinase matrix in relation to morbid obesity and associated pathologies

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ABSTRACT

Objectives: Matrix Metalloproteinases (MMPs), these calcium-dependent zinc-containing endopeptidases play an important role in adipogenesis and angiogenesis by modifying tissues and degrading the extracellular matrix (ECM). Matrix glycoproteins, gelatin, collagens, proteoglycans and elastin are all found in the ECM. Current meta-analysis confirmed the lower levels of IL-6 and CRP was found following bariatric surgery. Several studies have shown correlations between E-selectin levels, BMI, and MMP-9 levels. There was also a strong link between the metalloproteinases MMP-2 and MMP-9. MMP-2 and adiponectin levels are related. MMP-9 levels, on the other hand, were modestly linked with E-selectin and HDL cholesterol levels, as previously stated. Also current observations imply that alterations in the ECM caused by MMP-mediated degradation may be crucial for the differentiation of adipocytes. The most crucial component of this is that MMPs are involved in the remodeling of tissue after gastric bypass surgery, as revealed by these markers (especially MMP-2 and MMP-9). Thus, it is tempting to assume that adipocyte derived MMPs may constitute a novel pharmaceutical target for limiting adipose tissue development through the reduction of adipocyte differentiation and angiogenesis. MMP-2 exhibits far more accurate oscillations than MMP-9 during pre- and post-surgical weight fluctuations, and hence may be used as a predictor for gastric bypass success. The purpose of this paper is to conduct a comprehensive review of the literature with an emphasis on the critical functions that MMPs have in the pathophysiology of obesity and the related diseases.

Keywords: matrix metalloproteinase, morbid obesity, metabolic surgery, extracellular matrix

MMPs are calcium-dependent zinc-containing endopeptidases that play a role in adipogenesis and angiogenesis by modifying tissues and degrading the extracellular matrix (ECM). Matrix glycoproteins, gelatin, collagens, proteoglycans and elastin are all found in the ECM. MMPs are not normally highly produced in normal physiological settings; nonetheless, overexpression of MMPs disrupts the balance of MMP activity and tissue inhibitors of MMPs (TIMPs) resulting in a range of clinical diseases. MMPs are classified into over 25 distinct subtypes [1]. MMPs also break pericellular proteins and surface molecules, depending on the substrate, and are therefore implicated in cell behavior regulation [2].

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Obesity has been linked to an increase in the number of adipocytes and preadipocytes, as well as microvascular endothelial cells [3]. MMP-2 and MMP-9 are two essential enzymes involved in the modulation of the ECM and the production of adipocytes and preadipocytes, respectively. Obese people had higher MMP-2 and MMP-9 levels, which resulted in an altered ECM metabolism [4].

The purpose of this paper is to conduct a comprehensive review of the literature with an emphasis on the critical functions that MMPs have in the pathophysiology of obesity and the related diseases.

METHODS

The article is a narrative review based on a PubMed search of the English-language medical literature for essential elements of the stated goal so that we can create a global picture of the impact that MMPs have on morbid obesity and the conditions that accompany this pathology.

Obesity and Biologic Systemic Status

Systemic inflammation, infiltration of macrophages into adipose tissue, and ECM remodeling mediated by MMPs are all characteristics of obesity. Macrophage infiltration is an indication of adipose tissue inflammation caused by obesity [5]. Macrophage infiltration is also critical for the control of ECM turnover and fibrogenesis, both of which are mediated by various MMPs [6].

The same alterations have been seen in obesity-induced fatty liver macrophages [7]. There is still a need to gather further data to show a link between the expression of MMP in adipose and hepatic tissue. To create regions of fibrosis in an organ, it starts with an area of inflammation and an imbalance between ECM creation (that is, fibrogenesis) [8-10] and ECM breakdown (which is fibrinolysis) [11, 12].

De Meijer *et al*. [13] showed that a 60% fat diet might result in an increased fat index (a measure of obesity) and so promote obesity. Furthermore, it leads to insulin resistance and hepatic steatosis over time, both of which are linked to obesity [13].

Domienik-Karowicz *et al*. [14] demonstrated that the development of diet-induced obesity in an obesity-induced model was linked with an increase in the expression of MMPs in adipose tissue. The relevant MMPs are MMP2, MMP3, MMP8, MMP12, MMP13, ADAM17, TIMP1 and TIMP2 [14]. This result supports the findings of Lijnen *et al*. [15] and Chavey *et al*. [16]. The most consistent finding across most of the research was an elevation in MMP3, MMP8, MMP12, MMP13, and TIMP1 gene expression.

MMPs play an important part in the management of adipogenesis by performing proteolytic activities throughout adipose mass growth [17].

While our meta-analysis confirmed the lower levels of IL-6 and CRP following bariatric surgery, the mean difference for the modification of TNFa did not achieve statistical significance at any of the follow-up intervals. These cytokines are significant because they have a role in the pathophysiology of type 2 diabetes and coronary heart disease [18].

Additionally, MMPs are also involved in glucose homeostasis. Derosa *et al*. [19] discovered elevated MMP-2, MMP-9, TIMP-1, and TIMP-2 plasma levels in diabetic patients, indicating a disruption in ECM metabolism in diabetes. Boden *et al*. [20] observed that hyperinsulinemia enhances membrane MMP-1, MMP-2 and MMP-9 activity in aortic tissues in agreement with this concept.

MMP in Other Related Diseases

It is now well accepted that high adipose tissue formation is a risk factor in and of itself for hypertension, diabetes, atherosclerosis as well as cardiac and vascular dysfunction. Increased calorie intake combined with lower energy expenditure increases adipocyte substrate availability, resulting in hypertrophy [21].

ECM metalloproteinases (MMP-2 and MMP-9), E-selectin, adiponectin, CD40L and PAI-1, all have a role in atherosclerosis. Extracellular MMPs are engaged in ECM remodeling as well as basal membrane remodeling. Increased proteolysis and endothelial injury or matrix constituent buildup are determined by an imbalance between MMPs, their inhibitors, and α-2-macroglobulin. MMPs have been proven to play an important role in the atherosclerotic process, the regulation of adipogenesis, the blood vessels remodeling as well as cardiac muscle walls [6, 7].

Obesity progresses by a process of substantial remodeling of the adipose tissue that includes angiogenesis,

hyperplasia, and hypertrophy.

In contrast to other adipocyte-derived hormones, adiponectin has a negative correlation with visceral fat, BMI, and body weight, according to some authors, however numerous studies contradict this theory. In clinical practice, hypoadiponectinemia is a solid and favorable predictor of type II diabetes, lipid disorders, arterial hypertension, and nonalcoholic fatty liver disease [22].

Several studies have shown correlations between E-selectin levels, BMI, and MMP-9 levels. There was also a strong link between the metalloproteinases MMP-2 and MMP-9. MMP-2 and adiponectin levels are related. MMP-9 levels, on the other hand, were modestly linked with E-selectin and HDL cholesterol levels, as previously stated [4, 5].

The hypertrophy and hyperplasia of adipocytes have been extensively researched. The mechanisms behind these processes are not known at the moment. There is a paucity of evidence on the control of angiogenic processes and also the ECM modification during fat mass accumulation and the resolution of obesity throughout time. Adipocytes perform significant metabolic functions and are capable of producing a variety of substances, including growth factors and cytokines, that are involved in the paracrine control of adipose tissue remodeling. Adipocytes, on the other hand, release proangiogenic substances such as tumor necrosis factor-α, monobutyrin [23], leptin, and vascular endothelial growth factor (VGEF). ECM components are generated and destroyed during adipocyte development, and some investigations have shown that adipocyte differentiation is modulated by the ECM environment [11, 12, 17].

To confirm that the released MMPs originated from mature adipocytes, many tests were done on newly obtained mature adipocytes. RT-PCR study using primers specific for MMP-9 and MMP-2 cDNAs confirmed the existence of both transcripts in human adipocytes, but the expression of MMP-2 was much higher than MMP-9, while MMP-9 also had a significant individual variation. MMP-2 activity was considerably higher in human fat tissue than in MMP-9 activity. Additionally, under the same settings, both mature MMP-2 and pro–MMP-2 were found. MMP-9 increased somewhat throughout the first seven days of differentiation, reaching a peak on day 7, and then dropped [24-26].

As previously stated, MMP-2 and MMP-9 suppression reduce adipocyte development. Preadipocytes may represent the link between MMPs and adipocyte differentiation. To test if the MMP activity, secreted by adipocytes, has a role in differentiation, in the presence of adipogenic media, preadipocytes were treated with batimastat (0.5-10 mmol/l) escalating doses of MMP inhibitors, and captopril (100-1,000 mmol/l).

Bouloumie *et al*. [27] established for the first time that the adipose tissue of humans produces and secretes MMP-2 and MMP-9. Further investigation of MMPs secreted by adipocytes on the mouse preadipocyte indicates that MMP-9 and MMP-2 production and the release are higher throughout adipocyte development. These findings demonstrate unequivocally that MMPs are required for adipocyte development [27].

Despite what was previously stated, adipocytes demonstrated substantial interindividual variability, indicating that adipocyte-derived MMP production, secretion, and activity may be regulated by as-yet-unidentified modifying variables [28].

While the extracellular network of fibronectin and the network structures of laminin, as well as type IV collagen are damaged throughout the differentiation process of adipocyte, the network of type I collagen, which is the last to mature, remained intact. To understand why skin elasticity is affected both by obesity and weight reduction, it is important to understand the structural degradations in elastin, fibronectin and subcutaneous collagen [29, 30].

Taken together, the current observations imply that alterations in the ECM caused by MMP-mediated degradation may be crucial for the differentiation of adipocytes. Furthermore, given that TIMP inhibited angiogenesis induced by adipocyte conditioned medium, it is tempting to infer that MMPs may represent novel, intriguing therapeutic targets for monitoring adipose tissue growth by decreasing adipocyte differentiation and angiogenic processes [31].

There is evidence to support the production and release of MMP-9 and MMP-2 by human adipose tissue. Indeed, whereas MMP-2 activity was much greater than MMP-9 activity, both were detectable [32, 33].

The levels of MMP-9 were shown to be considerably greater in individuals with metabolic syndrome and obesity (BMI values) as compared to those with

no metabolic disorders as well as normal body weight. Derosa *et al*. [19], and other studies established a link between MMP-9 and body weight parameters in individuals with severe obesity before to and after bariatric surgery [34-36].

Not only are the advantages of bariatric surgery biological in nature, but they also seek to enhance one's quality of life. Several studies (Mirica *et al*. [12, 17]) reveal that the majority of patients who have bariatric surgery, increases their athletic performance and frequency, as well as their sexual status ($p < 0.05$). Additionally, 44% of patients improved their libido and intercourse quality. Bariatric surgery's less invasive method enables a rapid reintegration of the patient into regular activities [37, 38]. Bariatric surgery should be seen in terms of the benefits it provides to daily life [39-43].

MMPs in Diabetes

Along with weight loss, bariatric surgery may significantly improve glycemic control in obese with type II diabetes patients. As a result, it is also known as metabolic surgery. Additionally, the impact on type II diabetes and body weight varies according to the kind of bariatric surgery performed, although the precise processes behind these effects are unclear [44].

Numerous biological variables are considered to have a significant role in diabetes pathogenesis. Fetuin-A, for example, is a secretory protein made by the liver that binds to the insulin receptor blocking the insulin signaling and ultimately inducing in vitro insulin resistance. In humans, it is also connected with diabetes and insulin resistance. MMP-7 is another indicator of diabetes since it is capable of digesting ECM structural proteins. Additionally, it is required for the development of cancer, innate immunity, and inflammatory illnesses such as scleroderma. MMP-7 levels were also shown to be elevated in individuals with type II diabetes, diabetic diastolic dysfunction, diabetic renal illness. However, the precise process remains a mystery [45].

As shown in multiple investigations, the preoperative blood MMP-7 level correlates with preoperative age, obesity-related metabolic diseases and indicators of central obesity. Serum MMP-7 levels are increased in patients with liver steatosis, type II diabetes, cardiovascular disease, and abdominal obesity [46].

Diabetes affects the blood levels of fetuin-A and MMP-7 in obese persons. At one year following surgery, Roux-en-Y gastric bypass (RYGB), mini gastric bypass MGB, and sleeve gastrectomy (SG) all lowered circulating fetuin-A levels while simultaneously lowering glycemic levels and antidiabetic therapy dosages. On the contrary, as Yang *et al*. [22] demonstrated, after RYGB, MGB, or SG the circulating MMP-7 levels were constant.

MMPs in Vascular Remodeling

The production of new blood arteries (angiogenesis) is essential for tissue development, tissue repair, and, unfortunately, solid tumor growth. MMPs may play a role in angiogenesis in three ways: they can facilitate the migration of endothelial cells into adjacent tissues by removing the barrier of ECM, they can encourage it by freeing stored angiogenic substances, and they can deny it by creating-angiogenic breakdown products. Furthermore, during the development of newly created blood vessels, the equilibrium between MMPs and their inhibitors must be reestablished to promote basement membrane formation, endothelial cell differentiation, as well as quiescence [47-50].

MMPs may potentially suppress angiogenesis by producing anti-angiogenic peptides. Angiostatin is a plasminogen breakdown product produced by MMP-2, MMP-3, MMP-7, MMP-9, and MMP-12 [51-55]. However, the role of MMPs in inhibiting angiogenesis is unknown, even though they are unquestionably significant positive regulators of angiogenesis.

MMPs in Cancer

MMPs are abundant and are triggered more frequently in malignancies than in benign, normal, or even premalignant tissues, with the greatest levels of expression occurring near the tumor-stroma interface during an active invasion. MMP expression has been shown to correlate significantly positively with a variety of indications of poor prognosis in practically all kinds of cancer. Increased MMP levels may be regarded as an independent predictor of decreased disease-free survival as well as an overall survival factor. It has been proven that when MMP activity is elevated or TIMP activity is decreased, benign cells develop malignant features. Malignant cells may become less aggressive by lowering their MMP levels or limiting their activity.MMP-1, MMP-2, MMP-3, MMP-9, and

MMP-14 have all been associated as agonists of angiogenesis, tumor invasion, and metastasis, as was reviewed by Sternlicht *et al*. [56].

Because endothelial cells cannot penetrate the ECM if it is not degraded, malignant cells cannot spread above it if the ECM is not inhibited or degraded. Recent data shows that MMPs have a greater influence on cancer than simply removing physical barriers; several MMPs have been demonstrated to promote early cancer formation, with MMP-3 promoting late epithelial-mesenchymal phenotypic changes associated with more severe malignant behavior [57]. These findings support the hypothesis that MMPs may play a role in practically every stage of cancer development, both early and late. Certain MMPs may inhibit cancer development, whereas others may not be involved in cancer but clearly perform basic physiologic functions. These alternatives must be explored, and the processes behind MMPs' impact on cancer must be fully understood, in order to maximize the efficacy while limiting toxicity of treatment medicines.

DISCUSSION

MMPs play an important part in adipogenesis through their proteolytic activity during adipose tissue remodeling. Hanusch-Enserer [7] established in 2009 that MMPs and ECM play a direct role in adipogenesis. In 2015, Domienik-Karowicz [14] demonstrated that the development of diet-induced obesity is associated with an increase of MMP expression in adipose tissue [14]. Regarding the diet used to induce obesity in rats, de Meijer *et al*. [13, 31, 32] demonstrated that a high fat diet, 60%, can not only increase the fat index and cause obesity, but if used for a lengthy period of time, it can also increase insulin resistance and hepatic steatosis, both of which are directly associated to obesity.

The diet administered in the research from Mirica *et al*. [12] was a combination of a hypercaloric-hyperlipidemic diet as described by other authors, a diet currently consumed by most of the people in medium as well as high-developed countries, and a diet based on food that is hypercaloric, sweetened beverages and sweetened carbonated beverages. To achieve obesity, the rats were given 82 percent butter and glucose-enriched chocolate. This was supplemented with rat meal at the discretion of the researcher and ad libitum water enhanced with 35 g of sugar/100 g of water. Fast food and sugary carbonated beverages consumption are rapidly increasing in nowadays society, so the same circumstances were reproduced. The statistically significant difference in food intake between the research groups and the control group on a regular diet saw an increase with 162 grams, more than 50% the body weight of the control rats.

The literature is replete with data on numerous diets that produce comparable effects, the critical factor being the end weight at which records are kept. It is well established that if a patient is obese for an extended length of time, he will get diabetes as a direct result of the food-induced obesity. Mirica *et al*. [17] revealed statistically significant variations in preoperative blood glucose levels and weight between the control and study groups. The research demonstrates that cormparable discrepancies exist even between triglycerides (TGL) and cholesterol (CHO) levels. Postoperative weight and blood glucose measurements, as well as CHO and TGL values, all demonstrate a significant decrease in values compared with the preoperative ones. It is worth mentioning that, in addition to the surgical operation that accounts for the majority of these variations, all rats in the research groups were restored to their usual diets. The BS group weight loss was significantly different; weight loss was also significantly different in group B but did not approach the levels of the BS group. As a result, it was theorized that the difference in postoperative weight reduction between the B and BS groups was due to sulodexide administration. However, more investigations would be required to evaluate this hypothesis.

Sulodexide is not known to have a significant function in weight loss, and it was hypothesized that its effect on tissue remodeling via altering the state of MMPs is what accounts for the advantage group BS had in weight loss. Mannello *et al*. [58] further illustrate the role of sulodexide in the metabolism of MMP. All groups consuming a hyperglycemic diet had preoperative glycemic levels of more than 190 mg/dl, except the C group, which had a value of 121 mg/dl. Blood glucose levels in group B decreased statistically significantly from 207 ± 23 mg/dl preoperatively to 123 ± 10 mg/dl postoperatively measured at 28 days, demonstrating once again the tight relationship between glycemic status and obesity and the ability of

weight reduction to normalize the levels of blood glucose.

Cases of complete diabetic remission have also been described in the literature barely one month following surgery. A special remark should be made of group S, where the reduction in glycemia 28 days postoperatively was not statistically significant (reduction was from 198.4 ± 13.19 mg/dl to only 191.7 ± 8.71 mg/dl). This is because this group has not undergone weight-loss surgery and the sulodexide administered did not initially reduce blood glucose levels, albeit it did return to normal diet. It seems as if the standard diet is insufficient to alter the glycemic status or weight curve. The control group saw a little rise in glycemic mean, which is regarded to be typical for this measure. While group S had the highest pre and postoperative TGL levels, any suggestion that this was related to sulodexide administration is presently without scientific basis, since there is no clear relationship between TGL status and sulodexide. Following the procedure, TGL decreased in groups S, B and BS, with the largest and statistically significant declines occurring in groups B and BS.

In a 2014 research on Wistar rats, Lilis et. al. [59] obtained a maximum reduction of 70 mg/dl. Because CHO demands the same level of care and relevance as TGL, preoperative values were recorded across batches, but without statistical significance, the highest levels being reported in the S group. Following surgery, the B and BS levels reduced significantly, but only in the BS group it was a statistical significance difference. Postoperative CHO levels correlate favorably with postoperative TGL, glycemia and the postoperative weight in BS group, respectively. Kawano *et al*. [60] and Kalaivani et. al. [61] both showed substantial reductions in TGL and CHO after bariatric surgery, which were all connected with postoperative estimated body weight loss (% EBWL).

A massive meta-analysis consisting of 6131 patients revealed that bariatric/metabolic surgery was 9.8 to 15.8 times more effective than conventional treatment in terms of weight loss, CHO, TGL, fasting blood glucose reduction and glycosylated hemoglobin (HbA1C). These findings indirectly support the conclusion that surgical treatment of obese patients is successful for weight reduction and also for type II diabetes mellitus remission [62].

The research on MMPs roles in obesity is highly varied in terms of the MMPs implicated and their mechanics. The majority of research concur that MMP-1, MMP-2, MMP-8 and MMP-9 are the primary MMPs involved with obesity. If preoperative MMP-2 values in groups S, B and BS were larger than those in the C group, postoperative MMP-2 values in both B and BS groups declined dramatically, even reaching levels below those in the control group, C group. While both MMPs exhibited measurable levels, MMP-9's dynamics were very different from those of MMP-2, in that it progressed from a greater preoperative value to a decreased postoperative value for B and BS groups. The values in group S are comparable to those in group C.

Some studies in the literature have shown that corroborated this dynamic after bariatric surgery, regardless of the participants' gender or their association with hyperlipidemia, insulin resistance or hypertension. MMP-2 and MMP-9 both have a favorable correlation with weight reduction in the B and BS groups, but there is not any difference between them. Sulodexide has no statistically significant effect on MMP-2, but has a substantial but not statistically significant effect on MMP-9, with values in BS group being higher than group B.

Additionally, MMP-2 had a statistically significant positive correlation with the value of TGL both pre- and post-operatively, which did not apply for MMP-9, a biomarker that is less affected by CHO, TGL as well as glycemic alterations. However, a greater effect had the administration of sulodexide. Tchernof *et al*. [63] showed that in obese individuals, there are correlations between MMP status and the lipid state.

Although not totally free of risks, gastric bypass has a high weight loss efficiency of about 82% and a small complication rate of roughly 1%.

CONCLUSION

Metabolic surgery has been to be the most successful mean of weight reduction and improvement, if not complete remission, of obesity-related diseases. The most crucial component of this is that MMPs are involved in the remodeling of tissue after gastric bypass surgery, as revealed by these markers (especially MMP-2 and MMP-9). Thus, it is tempting to assume that adipocyte derived MMPs may constitute a novel

pharmaceutical target for limiting adipose tissue development through the reduction of adipocyte differentiation and angiogenesis. MMP-2 exhibits far more accurate oscillations than MMP-9 during pre- and post-surgical weight fluctuations, and hence may be used as a predictor for gastric bypass success. Improving the quality of life is strongly connected to weight loss, % EBWL, and hence postoperative BMI. Additionally, there is a link between an enhanced quality of life and an improved sexual life or an increased frequency of physical activity. Metabolic surgery's less invasive method enables a rapid reintegration of the patient into regular activities. Metabolic surgery should be seen in terms of the beneficial improvements it brings to daily life.

Authors' Contribution

Study Conception: RMM; Study Design: RMM, AM; Supervision: LZ, NI; Funding: ABV, DCC; Materials: ABV, DCC; Data Collection and/or Processing: RI, AR; Statistical Analysis and/or Data Interpretation: AR, RMM; Literature Review: OG, RMM; Manuscript Preparation: ABV, DCC, RMM and Critical Review: LZ, NI.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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REFERENCES

1. Lee YJ, Heo YS, Park HS, Lee SH, Lee SK, Jang YJ. Serum SPARC and matrix metalloproteinase-2 and metalloproteinase-9 concentrations after bariatric surgery in obese adults. Obes Surg 2014;24:604-10.
2. Sternlicht MD, Werb Z. How matrix metalloproteinases regulate cell behavior. Annu Rev Cell Dev Biol 2001;17:463-516.
3. Ress C, Tschoner A, Ciardi C, Laimer MW, Engl JW, Sturm W, et al. Influence of significant weight loss on serum matrix metalloproteinase (MMP)-7 levels. Eur Cytokine Netw 2010;21:65-70.
4. Deng ZB, Liu Y, Liu C, Xiang X, Wang J, Cheng Z, et al. Immature myeloid cells induced by a high-fat diet contribute to liver inflammation. Hepatology 2009;50:1412-20.
5. Popov Y, Schuppan D. Targeting liver fibrosis: strategies for development and validation of antifibrotic therapies. Hepatology 2009;50:1294-306.
6. Guldiken S, Demir M, Arikan E, Turgut B, Azcan S, Gerenli M, et al. The levels of circulating markers of atherosclerosis and inflammation in subjects with different degrees of body mass index: soluble CD40 ligand and high-sensitivity C-reactive protein. Thromb Res 2007;119:79-84.
7. Hanusch-Enserer U, Zorn G, Wojta J, Kopp CW, Prager R, Koenig W, et al. Non-conventional markers of atherosclerosis before and after gastric banding surgery. Eur Heart J 2009;30:1516-24.
8. Friedman SL. Mechanisms of hepatic fibrogenesis. Gastroenterology 2008;134:1655-69.
9. Bataller R, Brenner DA. Liver fibrosis. J Clin Invest 2005;115:209-18.
10. Schuppan D, Afdhal NH. Liver cirrhosis. Lancet 2008;371:838-51.
11. Mirica RM, Ionescu M, Mirica A, Ginghina O, Iosifescu R, Rosca A, et al. Quality of life assessment after bariatric surgery-- a single-center experience. Indian J Surg 2018;80:435-41.
12. Mirica RM, Ionescu M, Mirica A, Ginghina O, Iosifescu R, Rosca A, et al. The important roles of matrix metalloproteinases in the pathophysiology of obesity. Rev Chim 2017;68:1481-4.
13. de Meijer VE, Sverdlov DY, Le HD, Popov Y, Puder M. Tissue-specific differences in inflammatory infiltrate and matrix metalloproteinase expression in adipose tissue and liver of mice with diet-induced obesity. Hepatol Res 2012;42:601-10.
14. Domienik-Karłowicz J, Rymarczyk Z, Dzikowska-Diduch O, Lisik W, Chmura A, Demkow U, et al. Emerging markers of atherosclerosis before and after bariatric surgery. Obes Surg 2015;25:486-93.
15. Lijnen HR, Demeulemeester D, Van Hoef B, Collen D, Maquoi E. Deficiency of tissue inhibitor of matrix metalloproteinase-1 (TIMP-1) impairs nutritionally induced obesity in mice. Thromb Haemost 2003;89:249-55.
16. Claffey KP, Wilkison WO, Spiegelman BM. Vascular endothelial growth factor. Regulation by cell differentiation and activated second messenger pathways. J Biol Chem 1992;267:16317-22.
17. Mirica RM, Ionescu M, Mirica A, Ginghina O, Iosifescu R, Rosca A, et al. Matrix metalloproteinases in obesity after gastric bypass surgery -- an experimental study . Indian J Surg 2020. DOI: 10.1007/s12262-020-02462-x
18. Rao SR. Inflammatory markers and bariatric surgery: a meta-analysis. Inflamm Res 2012;61:789-807.
19. Derosa G, D'Angelo A, Scalise F, Avanzini MA, Tinelli C, Peros E, et al. Comparison between metalloproteinases-2 and -9 in healthy subjects, diabetics, and subjects with acute coronary syndrome. Heart Vessels 2007;22:361-70.
20. Boden G, Song W, Pashko L, Kresge K. In vivo effects of insulin and free fatty acids on matrix metalloproteinases in rat

aorta. Diabetes 2008;57:476-83.
21. Galis ZS, Khatri JJ. Matrix metalloproteinases in vascular remodeling and atherogenesis: the good, the bad, and the ugly. Circ Res 2002;90:251-62.
22. Yang PJ, Ser KH, Lin MT, Nien HC, Chen CN, Yan WS, et al. Diabetes associated markers after bariatric surgery: fetuin-A, but not matrix metalloproteinase-7, is reduced. Obes Surg 2015;25:2328-34.
23. Wilkison WO, Choy L, Spiegelman BM. Biosynthetic regulation of monobutyrin, an adipocyte-secreted lipid with angiogenic activity. J Biol Chem 1991;266:16886-91.
24. Kubo Y, Kaidzu S, Nakajima I, Takenouchi K, Nakamura F. Organization of extracellular matrix components during differentiation of adipocytes in long-term culture. In Vitro Cell Dev Biol Anim 2000;36:38-44.
25. Nakajima I, Yamaguchi T, Ozutsumi K, Aso H. Adipose tissue extracellular matrix: newly organized by adipocytes during differentiation. Differentiation 1998;63:193-200.
26. Kuri-Harcuch W, Argüello C, Marsch-Moreno M. Extracellular matrix production by mouse 3T3-F442A cells during adipose differentiation in culture. Differentiation 1984;28:173-8.
27. Bouloumié A, Sengenès C, Portolan G, Galitzky J, Lafontan M. Adipocyte produces matrix metalloproteinases 2 and 9: involvement in adipose differentiation. Diabetes 2001;50:2080-6.
28. Galis ZS, Sukhova GK, Lark MW, Libby P. Increased expression of matrix metalloproteinases and matrix degrading activity in vulnerable regions of human atherosclerotic plaques. J Clin Invest 1994;94:2493-503.
29. Newby AC. Matrix metalloproteinases regulate migration, proliferation, and death of vascular smooth muscle cells by degrading matrix and non-matrix substrates. Cardiovasc Res 2006;69:614-24.
30. Newby AC. Do metalloproteinases destabilize vulnerable atherosclerotic plaques? Curr Opin Lipidol 2006;17:556-61.
31. de Meijer VE, Sverdlov DY, Popov Y, Le HD, Meisel JA, Nose V, et al. Broad-spectrum matrix metalloproteinase inhibition curbs inflammation and liver injury but aggravates experimental liver fibrosis in mice. PLoS One 2010;5:e11256.
32. de Meijer VE, Le HD, Meisel JA, Akhavan Sharif MR, Pan A, Nosé V, et al. Dietary fat intake promotes the development of hepatic steatosis independently from excess caloric consumption in a murine model. Metabolism 2010;59:1092-105.
33. Ailhaud G, Grimaldi P, Négrel R. Cellular and molecular aspects of adipose tissue development. Annu Rev Nutr 1992;12:207-33.
34. Zangani D, Darcy KM, Masso-Welch PA, Bellamy ES, Desole MS, Ip MM. Multiple differentiation pathways of rat mammary stromal cells in vitro: acquisition of a fibroblast, adipocyte or endothelial phenotype is dependent on hormonal and extracellular matrix stimulation. Differentiation 1999;64:91-101.
35. Szczęsny W, Kuligowska-Prusińska M, Dąbrowiecki S, Szmytkowski J, Reśliński A, Słupski M. Activity of metalloproteinases and adiponectin in obese patients-a possible factor of incisional hernias after bariatric procedures. J Zhejiang Univ Sci B 2018;19:65-70.
36. Lau DC, Dhillon B, Yan H, Szmitko PE, Verma S. Adipokines: molecular links between obesity and atheroslcerosis. Am J Physiol Heart Circ Physiol 2005;288:H2031-41.
37. Krebs M, Geiger M, Polak K, Vales A, Schmetterer L, Wagner OF, et al. Increased plasma levels of plasminogen activator inhibitor-1 and soluble vascular cell adhesion molecule after triacylglycerol infusion in man. Thromb Haemost 2003;90:422-8.
38. Iribarren C. Lipoprotein-associated phospholipase A2 and cardiovascular risk: state of the evidence and future directions. Arterioscler Thromb Vasc Biol 2006;26:5-6.
39. Freedman JE. CD40 ligand--assessing risk instead of damage? N Engl J Med 2003;348:1163-5.
40. Hotamisligil GS, Shargill NS, Spiegelman BM. Adipose expression of tumor necrosis factor-alpha: direct role in obesity-linked insulin resistance. Science 1993;259:87-91.
41. Grzechocińska B, Dąbrowski FA, Sierdzinski J, Cyganek A, Wielgoś M. The association between serum metalloproteinase concentration, obesity, and hormone levels in reproductive-aged women. Endokrynol Pol 2019;70:49-56.
42. Blann AD, Lip GY. Hypothesis: is soluble P-selectin a new marker of platelet activation? Atherosclerosis 1997;128:135-8.
43. Marx N, Imhof A, Froehlich J, Siam L, Ittner J, Wierse G, et al. Effect of rosiglitazone treatment on soluble CD40L in patients with type 2 diabetes and coronary artery disease. Circulation 2003;107:1954-7.
44. Varo N, Vicent D, Libby P, Nuzzo R, Calle-Pascual AL, Bernal MR, et al. Elevated plasma levels of the atherogenic mediator soluble CD40 ligand in diabetic patients: a novel target of thiazolidinediones. Circulation 2003;107:2664-9.
45. Bermudez EA, Rifai N, Buring J, Manson JE, Ridker PM. Interrelationships among circulating interleukin-6, C-reactive protein, and traditional cardiovascular risk factors in women. Arterioscler Thromb Vasc Biol 2002;22:1668-73.
46. Henn V, Slupsky JR, Gräfe M, Anagnostopoulos I, Förster R, Müller-Berghaus G, et al. CD40 ligand on activated platelets triggers an inflammatory reaction of endothelial cells. Nature 1998;391:591-4.
47. Déchanet J, Grosset C, Taupin JL, Merville P, Banchereau J, Ripoche J, et al. CD40 ligand stimulates proinflammatory cytokine production by human endothelial cells. J Immunol 1997;159:5640-7.
48. Slupsky JR, Kalbas M, Willuweit A, Henn V, Kroczek RA, Müller-Berghaus G. Activated platelets induce tissue factor expression on human umbilical vein endothelial cells by ligation of CD40. Thromb Haemost 1998;80:1008-14.
49. Zhou L, Stordeur P, de Lavareille A, Thielemans K, Capel P, Goldman M, et al. CD40 engagement on endothelial cells promotes tissue factor-dependent procoagulant activity. Thromb Haemost 1998;79:1025-8.
50. Silva SA, Gobbo MG, Pinto-Fochi ME, Rafacho A, Taboga SR, Almeida EA, et al. Prostate hyperplasia caused by long-term obesity is characterized by high deposition of extracellular matrix and increased content of MMP-9 and VEGF. Int J Exp Pathol 2015;96:21-30.
51. André P, Prasad KS, Denis CV, He M, Papalia JM, Hynes RO, et al. CD40L stabilizes arterial thrombi by a beta3 integrin--dependent mechanism. Nat Med 2002;8:247-52.
52. Henn V, Steinbach S, Büchner K, Presek P, Kroczek RA. The inflammatory action of CD40 ligand (CD154) expressed on ac-

tivated human platelets is temporally limited by coexpressed CD40. Blood 2001;98:1047-54.
53. Kräling BM, Wiederschain DG, Boehm T, Rehn M, Mulliken JB, Moses MA. The role of matrix metalloproteinase activity in the maturation of human capillary endothelial cells in vitro. J Cell Sci 1999;112 (Pt 10):1599-609.
54. Owolabi US, Amraotkar AR, Coulter AR, Singam NSV, Aladili BN, Singh A, et al. Change in matrix metalloproteinase 2, 3, and 9 levels at the time of and after acute atherothrombotic myocardial infarction. J Thromb Thrombolysis 2020;49:235-44.
55. Tuomainen AM, Nyyssönen K, Laukkanen JA, Tervahartiala T, Tuomainen TP, Salonen JT, et al. Serum matrix metalloproteinase-8 concentrations are associated with cardiovascular outcome in men. Arterioscler Thromb Vasc Biol 2007;27:2722-8.
56. Sternlicht MD, Bergers G. Matrix metalloproteinases as emerging targets in anticancer therapy: status and prospects. Emerging Ther Targets 2000;4:609-33.
57. Lochter A, Galosy S, Muschler J, Freedman N, Werb Z, Bissell MJ. Matrix metalloproteinase stromelysin-1 triggers a cascade of molecular alterations that leads to stable epithelial-to-mesenchymal conversion and a premalignant phenotype in mammary epithelial cells. J Cell Biol 1997;139:1861-72.
58. Mannello F, Medda V, Ligi D, Raffetto JD. Glycosaminoglycan sulodexide inhibition of MMP-9 gelatinase secretion and activity: possible pharmacological role against collagen degradation in vascular chronic diseases. Curr Vasc Pharmacol 2013;11:354-65.
59. Lillis J, Kendra KE. Acceptance and Commitment Therapy for weight control: Model, evidence, and future directions. J Contextual Behav Sci 2014;3:1-7.
60. Kawano Y, Ohta M, Hirashita T, Masuda T, Inomata M, Kitano S. Effects of sleeve gastrectomy on lipid metabolism in an obese diabetic rat model. Obes Surg 2013;23:1947-56.
61. Kalaivani A, Uddandrao VVS, Parim B, Saravanan G, Nivedha PR, Sushma CK, et al. Reversal of high fat diet-induced obesity through modulating lipid metabolic enzymes and inflammatory markers expressions in rats. Arch Physiol Biochem 2019;125:228-34.
62. Esquivel AL, Pérez-Ramos J, Cisneros J, Herrera I, Rivera-Rosales R, Montaño M, et al. The effect of obesity and tobacco smoke exposure on inflammatory mediators and matrix metalloproteinases in rat model. Toxicol Mech Methods 2014;24:633-43.
63. Tchernof A, Després JP. Pathophysiology of human visceral obesity: an update. Physiol Rev 2013;93:359-404.