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Review

Modulating Matrix Metalloproteinase Activity in Obesity: Comparative Effects of Bariatric Surgery and GLP-1/GIP-Based Pharmacotherapy

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Abstract

Obesity is a multifactorial metabolic disease characterized by chronic low-grade inflammation, extracellular matrix (ECM) dysfunction, and systemic metabolic dysregulation. Matrix metalloproteinases (MMPs), especially MMP-2 and MMP-9, are key regulators of ECM remodeling and inflammation in obesity. This narrative review aimed to synthesize current evidence on the effects of bariatric surgery and pharmacological therapies, including GLP-1 and dual GLP-1/GIP receptor agonists, on MMP activity and metabolic outcomes. Literature from PubMed and Scopus (2015–2024) was analyzed, focusing on studies evaluating MMPs, inflammation, and metabolic parameters. Bariatric surgery consistently reduces MMP-9 levels and normalizes MMP-2 activity, contributing to improved ECM integrity, reduced inflammation, and enhanced insulin sensitivity. Pharmacological therapies achieve substantial weight loss and glycemic control but evidence regarding their direct effects on MMP activity remains limited. This review highlights bariatric surgery as the most effective strategy for modulating obesity-related MMP dysregulation and emphasizes the need for further research into the mechanistic effects of modern pharmacotherapy on ECM remodeling.

Keywords: obesity; bariatric surgery; GLP-1; GIP; matrix metalloproteinases; inflammation; extracellular matrix

1. Introduction

Obesity is one of the most pressing global health challenges of the 21st century, associated not only with excess body weight but also with severe comorbidities such as type 2 diabetes mellitus (T2DM), hypertension, cardiovascular disease, and several malignancies. Beyond energy imbalance, obesity is increasingly recognized as a state of chronic low-grade inflammation that promotes metabolic dysfunction and accelerates disease progression.

Extracellular matrix (ECM) remodeling plays a central role in the pathophysiology of obesity. Structural and functional alterations in adipose tissue, including fibrosis, hypoxia, and dysregulated angiogenesis, are driven by imbalances in ECM homeostasis. Matrix metalloproteinases (MMPs), a family of zinc-dependent endopeptidases, are pivotal mediators of ECM degradation and tissue remodeling. Among them, MMP-2, MMP-9, and MMP-14 are particularly important due to their links with systemic inflammation, insulin resistance, and vascular complications.

Bariatric surgery is currently the most effective therapeutic strategy for obesity, leading to profound weight reduction and remission of metabolic comorbidities. Recent evidence suggests that its beneficial effects may be partly mediated by modulation of MMP activity. Meanwhile, pharmacological therapies, such as GLP-1 receptor agonists and dual GLP-1/GIP agonists, represent

promising less invasive alternatives. However, their impact on ECM remodeling and MMP activity remains poorly understood.

This narrative review aims to compare the effects of bariatric surgery and modern pharmacotherapy on MMP activity and metabolic outcomes. A literature search was conducted in PubMed and Scopus for articles published between 2015 and 2024, including experimental studies, clinical trials, and meta-analyses addressing MMPs, obesity, and treatment outcomes. By synthesizing current knowledge, this review highlights the role of MMPs in obesity pathogenesis and discusses the therapeutic potential of targeting ECM remodeling.

2. Materials and Methods

This review was conducted as a narrative synthesis of the current evidence. A structured literature search was performed in PubMed, Scopus, and Web of Science databases for articles published between January 2015 and March 2024. Search terms included combinations of “matrix metalloproteinase” OR “MMP” AND “obesity,” “bariatric surgery,” “GLP-1 receptor agonist,” “GIP agonist,” and “pharmacotherapy.” Additional references were identified by manual screening of bibliographies of relevant reviews and clinical trials. Both experimental (in vitro and animal studies) and clinical studies (randomized controlled trials, cohort studies, systematic reviews, and meta-analyses) were considered. Articles not written in English, case reports, and conference abstracts without peer review were excluded.

3. Matrix Metalloproteinases in Obesity

The complex role of MMPs in obesity reveals their significant impact on ECM remodelling, inflammation and metabolic disorders. Investigating the function of MMPs provides a basis for further investigation of obesity associated inflammation and the development of options for therapeutic intervention. This section highlights how the activity of MMPs interacts not only with adipose tissue dynamics, but also with their impact on more extensive metabolic pathways.

3.1. Role and Function of MMPs

Extracellular matrix metalloproteinases (MMPs), zinc-dependent endopeptidases, play an essential role in ECM remodelling. They influence tissue homeostasis, angiogenesis and immune system. Dysregulated MMP activity contributes to pathological remodelling of the ECM. This leads, to significant structural and functional impairments in adipose tissue, infiltration of immune cells, exacerbates local inflammation. These changes result in tissue fibrosis and increased rigidity of cell membranes, which hinders proper adipocyte expansion and ultimately promotes ectopic lipid deposition in tissues other than adipose. It highlights the role of MMPs not only in structural remodelling, but also as modulators of metabolic dysfunction (Ruiz-Ojeda et al., 2019; Mirica et al., 2022). The mechanisms by which MMPs affect ECM remodelling are closely linked to the degradation of specific components such as collagens, elastin and fibronectin. Dysregulated angiogenesis, driven by altered MMP activity, further exacerbates local hypoxia and promotes inflammation, creating a vicious cycle that accelerates adipose tissue dysfunction in obesity (Ruiz-Ojeda et al., 2019; Li et al., 2020).

Among various MMPs associated with obesity, MMP-2 and MMP-9 stand out due to their significant expression in adipocytes and their key role in ECM degradation. Elevated levels of these MMPs are closely associated with systemic inflammation and insulin resistance, which are observed in obesity. Their activity promotes pathological changes in adipose tissue by breaking down structural components of the ECM, thereby facilitating macrophage infiltration and potentiating local inflammation. Such processes contribute to a pro-inflammatory microenvironment, with long-term consequences for glucose metabolism (Wu et al., 2020; Mirica et al., 2022). Studies distinguish between MMP mRNA expression and protein concentrations. The paradoxical observation of increased MMP-9 protein levels despite decreased mRNA expression highlights potential post-

transcriptional regulatory mechanisms that require further investigation (Aksoyer Sezgin et al., 2022). A deeper investigation of these regulatory mechanisms may provide new insights into how MMPs act at different biological levels, potentially revealing new points of intervention in the treatment of obesity. Similarly, MMP-2 protein levels tend to be elevated in obese patients, its gene expression may be downregulated, indicating potential post-transcriptional modifications or differences in protein stability and activation (Aksoyer Sezgin et al., 2022). What's more, the correlation between MMP-2 activity and components of the metabolic syndrome, such as BMI, body weight and fasting blood glucose, highlights its significant role in obesity pathology, promoting it as a viable target for therapeutic development (Aksoyer Sezgin et al., 2022). Furthermore, MMP-2 was described as risk factor of leptin resistance in obesity, a major barrier to effective metabolic regulation. MMP-2 cleaves the extracellular domain of leptin receptors in the hypothalamus, disrupting leptin signaling pathways, impairing appetite regulation and energy homeostasis. The present process predisposes to the development of obesity by increasing food intake and, consequently, the accumulation of fatty components. Experimental in vivo mouse model have shown that silencing MMP-2 activity, through lentivirus delivery or genetic deletion, restores leptin receptor function and reduces fat mass, providing compelling evidence for MMP-2-targeted treatment as a potential therapeutic strategy (Mazor et al., 2018). Astrocytes and agouti-related peptide (AgRP) neurons in the hypothalamus are key sources of MMP-2 secretion, highlighting the unique link between ECM remodeling and central nervous system dysfunction. These reports extend the traditional understanding of MMPs by linking their activity to central metabolic regulation, illustrating their systemic impact on obesity progression and highlighting their importance as therapeutic targets (Mazor et al., 2018).

MMP-14 plays a dual role in development of obesity, depending on the duration of the disease. In the early stages of obesity, its activation promotes adipocyte expansion by reducing ECM "stiffness" and alleviating mechanical stress, thus providing metabolic benefits. However, in advanced obesity, MMP-14 overexpression contributes to fibrosis and inflammation through the production of endotrophin, a by product that exacerbates insulin resistance and impairs lipid metabolism. MMP-14 overexpression is also associated with reduced energy expenditure and metabolic failure in transgenic models, further complicating its therapeutic modulation. These opposing roles underscore the complexity of MMP-14's involvement in obesity, requiring stage-specific therapeutic strategies to harness its positive effects while mitigating its deleterious effects (Li et al., 2020). Further on, abdominal white adipose tissue shows increased levels of MMP-3, MMP-11, MMP-12, and MMP-14, which are associated with ECM remodeling and inflammation. Conversely, MMP-7 and MMP-9 are downregulated in it, suggesting compensatory mechanisms or the involvement of alternative regulatory pathways depending on the type of adipose tissue. (Ruiz-Ojeda et al., 2019; Li et al., 2020). The differential expression of pro-inflammatory and anti-inflammatory MMPs and their implications for ECM dynamics further underscore the importance of spatial and temporal considerations in studying MMP activity (Ruiz-Ojeda et al., 2019). Understanding these mechanisms is key to using MMP modulation as a potential therapeutic approach to treat obesity and its multifaceted pathophysiology.

MMP	Main biological action	Effect on obesity / pathophysiological mechanisms	Clinical significance	Sources
MMP-2	Degradation of collagen IV, elastin, fibronectin; ECM remodelling	- ↑ Elevated in obesity - Associated with BMI, glucose, body weight	Therapeutic target – its inhibition improves leptin signalling and	Mazor 2018; Aksoyer Sezgin 2022

		- Causes leptin resistance by cutting the leptin receptor in the hypothalamus	insulin resistance	
MMP-9	Degradation of collagen IV and gelatinase; macrophage infiltration	- ↑Elevated in obesity - Correlates with CRP, IL-6, TNF- α - Promotes inflammation and endothelial dysfunction	↓ Decreases after bariatric surgery → reduction in cardiovascular risk	Mirica 2022; García-Prieto 2019; Ozen 2018
MMP- 8	Degradation of type I collagen; regulation of inflammatory response	- Decreases after bariatric surgery - Associated with a decrease in leptin - Correlates with improved glycaemia and HbA1c	It may be a marker of early metabolic improvement after surgery.	Liberale 2017
MMP-14 (MT1-MMP)	Activation of pro-MMP-2; ECM remodelling; endotrophin production	- In early obesity, it promotes adipocyte expansion (beneficial) - In advanced obesity → fibrosis, endotrophin, insulin resistance	Effect dependent on stage of obesity; potential target for staged therapy	Li 2020
MMP-3	Regulation of other MMPs; degradation of proteoglycans	- ↑ Increased in abdominal adipose tissue - May promote inflammatory processes	Limited clinical data; further research is required.	Ruiz-Ojeda 2019
MMP-7	Degradation of proteoglycans and ECM components	- ↓ Reduced in adipose tissue in obesity (compensatory mechanisms)	Potential protective role in ECM	Ruiz-Ojeda 2019
MMP-11	ECM remodelling and adipocyte differentiation	- ↑ Elevated in the adipose tissue of obese individuals	Early marker of metabolic disorders	Ruiz-Ojeda 2019

		- Contributes to metabolic dysfunction		
MMP-12	Macrophage elastase; elastin degradation	- ↑ Elevated in adipose tissue - Associated with macrophage infiltration	May worsen adipose tissue fibrosis	Ruiz-Ojeda 2019
TIMPs (1–4)	Natural MMP inhibitors	- TIMP/MMP imbalance → predominance of ECM degradation	ECM stability and inflammation progression index	Boumiza 2021

3.2. Obesity-Related Inflammation

Obesity is linked to chronic low-grade inflammation, which significantly contributes to its associated metabolic dysfunctions and complications. This inflammatory state is characterized by an overproduction of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF- α), interleukin-1 beta (IL-1 β), and interleukin-6 (IL-6), primarily generated by macrophages infiltrating dysfunctional adipose tissue. These cytokines not only regulate adipocyte turnover through proliferation and apoptosis but also accelerate ECM remodelling. They upregulate MMPs like MMP-2 and MMP-9, which, in turn, degrade ECM components and perpetuate systemic inflammation (Wang & He, 2018; Mirica et al., 2022). This inflammatory cascade establishes a feedback loop, further exacerbating adipose dysfunction and metabolic disturbances. Notably, disrupted ECM stability parallels an increase in systemic inflammatory markers, highlighting the interplay between local tissue inflammation and widespread metabolic effects. Pre-inflammatory macrophages are a key driver of inflammation in obesity. Among them, M1 macrophages predominate, contributing mainly to the pro-inflammatory state by replacing anti-inflammatory M2 macrophages. This substitution intensifies the inflammatory environment in overdeveloped adipose tissue, thereby increasing the production of cytokines such as TNF- α and IL-1 β , which have systemic effects on insulin signaling pathways leading to insulin resistance (Freitas Jr. et al., 2018; Henning, 2021),(Henning, 2021; Wang & He, 2018). In addition to adipose tissue, these cytokines exert their effects on vascular tissues, further stimulating MMP production, thus correlating local immune cell activity with systemic vascular inflammation and increased risk of cardiovascular complications (Ozen et al., 2018). The systemic spread of localized inflammation underscores the seriousness of macrophage-driven processes, justifying more targeted interventions to modulate macrophage phenotypes and their contribution to metabolic disorders. The imbalance between pro-inflammatory M1 macrophages and anti-inflammatory M2 macrophages further exacerbates the release of cytokines, including elevated levels of TNF- α and IL-1 β . These cytokines show a strong correlation with systemic markers of inflammation, such as high levels of C-reactive protein (CRP) and IL-6, which are hallmarks of obesity (Wang & He, 2018; Freitas Jr. et al., 2018). This chronic state of immune activation and cytokine overproduction disrupts normal lipid metabolism, exacerbates hyperlipidemia, and increases the risk of developing type 2 diabetes. Obesity-induced inflammation is not limited to macrophage involvement but also involves interactions with T lymphocytes that penetrate adipose tissue. CD8+ T cells, play a key role in macrophage activation, thereby increasing cytokine production and perpetuating metabolic disorders such as insulin resistance (Henning, 2021; Wang & He, 2018).

MMPs, such as MMP-2 and MMP-9, are integral to ECM remodeling in adipose tissue by-obesity-related inflammation and vascular complications. MMP-2 and MMP-9, play a central role in the

pathophysiological link between chronic low-grade inflammation and obesity-related metabolic complications. Inflammatory mediators such as TNF- α , IL-1 β , and IL-6, which are elevated in obese individuals, stimulate the expression and activation of MMPs. These enzymes degrade essential components of the extracellular matrix (ECM), including collagens and fibronectin, disrupting tissue architecture and enhancing the infiltration of immune cells into adipose tissue (Mirica et al., 2022; Ozen et al., 2018). This process leads to further inflammation, fibrosis, and impaired insulin signaling—hallmarks of metabolic dysfunction. MMP-2 and MMP-9 levels are consistently elevated in obesity and positively correlate with systemic inflammatory markers such as C-reactive protein (CRP), IL-6, and TNF- α . Their overexpression facilitates pathological ECM remodeling, which impairs adipocyte function and contributes to insulin resistance and type 2 diabetes (Mirica et al., 2022). MMP-9, in particular, is associated with vascular damage and endothelial dysfunction, acting as a molecular link between metabolic inflammation and cardiovascular disease (Ozen et al., 2018; Freitas Jr. et al., 2018). Disturbed MMP activity also affects vascular integrity by increasing endothelial permeability and promoting pro-atherogenic changes. Prostaglandin E2 (PGE2), a pro-inflammatory lipid mediator that is elevated in obese individuals, also plays a significant role in increasing MMP production. PGE2 levels correlate positively with CRP and MMP-1 activity, particularly in women, illustrating the gender-specific details of obesity-related inflammation and its metabolic consequences (Ozen et al., 2018; Henning, 2021). Elevated PGE2 levels contribute to vascular inflammation by modulating the behavior of adipocytes and immune cells, promoting the production of cytokines and MMPs, and impairing ECM stability. These effects exacerbate systemic metabolic dysfunction, further linking PGE2 to complications of obesity (Ozen et al., 2018; Henning, 2021). Whereas, MMP-9 is strongly associated with vascular damage and atherosclerosis, and its decrease after bariatric surgery correlates with improvements in vascular and metabolic aspects (Mirica et al., 2022; Freitas Jr. et al., 2018).

Taken together, the inflammatory upregulation of MMPs reinforces a feed-forward loop that sustains systemic inflammation, promotes adipose tissue dysfunction, accelerates the onset of metabolic diseases and vascular permeability increasing the risk of cardiovascular incidents in obese individuals (Ozen et al., 2018; Henning, 2021). Modulation of MMPs represents a promising therapeutic avenue for addressing the complex interplay between inflammation, ECM remodeling, and metabolic disease.

Inflammatory factor	Site of release	Effect on MMPs	Metabolic/clinical effect	Sources
TNF- α	M1 macrophages, adipocytes	$\uparrow$ MMP-2, $\uparrow$ MMP-9	Insulin resistance, ECM degradation, inflammation progression	Wang & He 2018; Mirica 2022
IL-1 β	M1 macrophages	$\uparrow$ MMP-2, $\uparrow$ MMP-9	Adipose tissue fibrosis, impaired insulin signalling	Henning 2021
IL-6	Adipocytes, immune cells	$\uparrow$ MMP-9	Systemic inflammatory response, $\uparrow$ CRP, risk of T2DM	Wang & He 2018
PGE2	Adipocytes, vascular tissue	$\uparrow$ MMP-1, $\uparrow$ MMP-2	Vasculitis, $\uparrow$ risk of atherosclerosis	Ozen 2018

CRP	Liver (induced by IL-6)	Correlates with MMP-2 and MMP-9	Marker of inflammation and cardiovascular complications	Freitas Jr. 2018
M1 macrophages	Infiltration of adipose tissue	Stimulate MMP-2, MMP-9	Progression of insulin resistance, adipocyte dysfunction	Henning 2021
M2 macrophages	Physiological adipose tissue	No stimulation of MMPs	Protective effect, reduction of inflammation – reduced in obesity	Henning 2021

4. Impact of Bariatric Surgery

Bariatric surgery is currently the most effective treatment for obesity. The next parts of this thesis describe how surgical procedures affect MMP activity and show their role in changing the structure and function of fat tissue.

4.1. Effects on MMP Activity

The relationship between bariatric surgery and MMPs activity has been investigated - revealing significant effects on inflammatory and metabolic pathways in obese patients. Studies show a significant reduction in MMP-9 levels, following surgical interventions. García-Prieto et al (2019) showed with a strong positive correlation between a reduction in active MMP-9 and a decrease in BMI. This observation suggests that weight loss achieved by bariatric surgery has a direct regulatory effect on MMP-9 activity, thereby attenuating inflammation and promoting improved metabolic outcomes. The authors highlighted the close relationship between adipose tissue remodelling and systemic markers of inflammation. Elevated MMP-9 levels are consistently associated with systemic inflammation and pathological ECM remodelling in obesity. Reducing MMP-9 activity with bariatric surgery not only reduces pro-inflammatory processes but also contributes to cardiovascular risk reduction (García-Prieto et al., 2019; Ozen et al., 2018). The impact of bariatric surgery is also observed in terms of MMP-2. Although the initial MMP-2 activity did not differ significantly between the study group and the control group García-Prieto et al. (2019) observed a significant reduction in MMP-2 levels after surgical intervention. The normalisation of MMP-2 activity suggests that weight loss reduces inflammatory processes at the tissue level. The upregulation of MMP-2 levels is consistent with findings of its association with BMI, body weight and fasting blood glucose levels (Aksoyer Sezgin et al., 2022). By attenuating MMP-2 activity, bariatric surgery demonstrates the broader anti-inflammatory capacity of surgical procedures, implying their systemic effects on pathways mediated by inflammation (Wu et al., 2020; García-Prieto et al., 2019). The complexity of MMP regulatory mechanisms in obesity was highlighted by Aksoyer Sezgin et al (2022), who demonstrated a paradoxical relationship between MMP gene expression and protein activity. Their findings revealed that despite reduced MMP-2 and MMP-9 gene expression, protein levels of these MMPs were elevated in adipose tissue, suggesting significant post-transcriptional regulation. This dynamic complicates the assessment of MMP activity, as protein levels and enzymatic activity must be assessed to fully appreciate the biological outcomes of bariatric surgery interventions. These findings highlight the need to study the effects of bariatric surgery on MMP activity at multiple biological levels, as changes in gene expression, protein activity and systemic and local influences may not be clear (Aksoyer Sezgin et al., 2022; García-Prieto et al., 2019). This intricacy calls for deeper research into the pathways regulating MMP expression and activity to elucidate how surgical weight loss

mediates its anti-inflammatory and metabolic effects. Further insights on MMPs were provided by Liberale et al (2017), who observed a significant reduction in MMP-8 levels after bariatric surgery, particularly in pathologically obese patients with type 2 diabetes mellitus (T2DM). This reduction was associated with a decrease in leptin levels, illustrating the interplay between adipokine regulation and MMP activity. Importantly, reduced MMP-8 levels correlated with significant improvements in metabolic parameters such as fasting glucose and glycated hemoglobin levels. These findings highlight the role of MMP-8 in early metabolic adaptations after bariatric interventions. The observed correlation between leptin and MMP-8 reductions illustrates how bariatric surgery simultaneously transforms inflammatory and metabolic pathways, providing further evidence of the interconnected nature of these systems (Liberale et al., 2017; Ozen et al., 2018). In contrast, Wu et al (2020) reported no significant changes in plasma levels of MMP-2, MMP-7 and MMP-9 after bariatric surgery procedures such as gastric bypass and sleeve gastrectomy, even after two years of follow-up. This discrepancy in information emphasises the variability of individual responses to surgery and the prospective impact of different methodologies and baseline patient characteristics. The dissonance with other studies suggests that MMP activity may not respond uniformly to bariatric surgery, highlighting the complexity of systemic and local MMP modulation. As highlighted by Wu et al (2020), improvements in obesity-related outcomes may be mediated by mechanisms independent of these MMPs, further highlighting the possibility of exploring alternative pathways influenced by surgical procedures. More randomised studies are needed to clarify the interaction of local and systemic inflammatory environments (García-Prieto et al., 2019; Aksoyer Sezgin et al., 2022).

Ozen et al. (2018) provided additional insights into inflammation's impact on MMP activity, particularly through elevated prostaglandin E2 (PGE2) levels in obese patients. They highlighted that PGE2 significantly upregulates MMP-1 and MMP-2, contributing to vascular wall remodeling and systemic metabolic dysfunctions. The anti-inflammatory effects of bariatric surgery, such as reductions in C-reactive protein (CRP) and other markers, indirectly imply the procedure's potential to suppress PGE2-mediated MMP activity, thus benefiting metabolic and vascular health. By addressing systemic inflammation, bariatric surgery appears to mitigate the adverse effects of chronic inflammation on MMP activity, creating a cascade of improvements at the molecular and metabolic levels (Ozen et al., 2018; Wu et al., 2020). The interconnected roles of inflammation, PGE2, and MMPs underline the multifactorial benefits of bariatric surgery, demonstrating its capacity to address obesity-related complications across multiple pathways.

In conclusion, the effect of bariatric surgery on MMP activity is multifaceted and provides significant benefits in reducing inflammation. However, the divergence of results across studies highlights the complexity of MMP regulation in obesity and the need for further research to fully elucidate the mechanisms involved. The interplay between inflammatory mediators, adipokines and ECM remodelling processes offers promising opportunities to understand and improve the outcomes of surgical interventions.

4.2. Metabolic Outcomes

The impact of bariatric surgery on metabolic outcomes in severe obesity is complex. Surgery markedly reduces systemic inflammation, confirmed by consistent declines in CRP, hs-CRP and ferritin, which strongly correlate with weight loss and T2DM remission (Lautenbach et al., 2021). The normalization of ferritin reflects reduced oxidative stress, while patients losing more than 50% of excess weight achieve the greatest improvements in inflammatory markers, showing that the degree of weight loss is a key determinant of success.

Another striking effect is the rapid improvement in glycaemic control. Within days, HOMA-IR may fall by 50%, and many patients experience partial or complete remission of T2DM (Biobaku et al., 2020). These early changes are linked to lower IL-6 and TNF- α , significant weight loss and improved insulin sensitivity (Osorio-Conles et al., 2021). Higher remission rates are observed in

patients with shorter disease duration, suggesting greater benefits from early surgical intervention. Still, variable outcomes point to additional influences such as genetics and comorbidities.

Bariatric surgery also improves lipid metabolism, with reductions in glucose, triglycerides, total and LDL cholesterol, and rises in HDL observed within six months (Freitas Jr. et al., 2018). These improvements parallel decreases in CRP and TNF- α (Mirica et al., 2022). Sustained weight loss amplifies these effects and lowers cardiovascular risk.

Long-term benefits include reduced visceral and subcutaneous fat, smaller adipocytes and improved insulin sensitivity, all contributing to durable metabolic health (Osorio-Conles et al., 2021). However, evidence on long-term changes in MMP activity remains limited. Since MMPs and TIMPs influence ECM remodeling, inflammation and vascular integrity, further research may clarify their role in sustaining metabolic improvements (Lautenbach et al., 2021; Boumiz et al., 2021).

In summary, bariatric surgery profoundly improves metabolic outcomes by reducing inflammation, enhancing insulin sensitivity, improving lipid profiles and potentially modulating MMP activity. While the benefits are clear, individual variability and gaps in long-term mechanistic data highlight the need for continued investigation and more personalized approaches.

5. Pharmacological Treatment Options

Pharmacological therapies offer important alternatives or complements to surgery. While bariatric surgery remains the most effective intervention for inducing sustained weight loss and remission of obesity-related comorbidities, pharmacological options provide a less invasive approach for patients not eligible for surgery or those experiencing postoperative weight regain. These therapies not only facilitate weight reduction and glycemic control but also offer potential benefits in modulating systemic inflammation and improving cardiometabolic risk.

Bariatric surgery is associated with robust anti-inflammatory effects, including significant reductions in CRP, TNF- α , and IL-6, as well as favorable changes in ECM remodeling markers such as MMPs. Studies by Freitas Jr. et al. (2018), Biobaku et al. (2020), and Wu et al. (2020) emphasize its efficacy in reducing systemic inflammation, improving cardiovascular and metabolic health, and promoting remission of T2DM, with reported remission rates reaching up to 80–90%. These effects are largely attributed to the substantial and sustained weight loss (25–30%) and hormonal shifts following surgery.

Although pharmacological therapies do not yet match the broad systemic effects of surgery, they continue to evolve. Notably, GLP-1 receptor agonists and dual agonists such as tirzepatide have demonstrated significant clinical utility in obesity management.

GLP-1 Receptor Agonists and Dual Receptor Agonists

GLP-1 receptor agonists (e.g. semaglutide, liraglutide) and dual agonists like tirzepatide effectively reduce weight and improve glucose metabolism. Tirzepatide, acting on both GLP-1 and Glucose-dependent Insulinotropic Polypeptide (GIP) receptors, shows superior outcomes—up to $\geq 15\%$ weight loss—compared to GLP-1 agonists alone (Pan et al., 2024). Pharmacological agents achieve 8–21% weight loss versus 25–30% seen with surgery (Elmaleh-Sachs et al., 2023). GLP-1 agonists reduce appetite and delay gastric emptying, while dual agonists offer enhanced efficacy. Tirzepatide significantly lowers Hemoglobin A1c (HbA1c) and improves cardiometabolic markers such as body weight, cardiovascular events, blood pressure, and lipid profile (Frías et al., 2021).

Comparative studies confirm tirzepatide's superiority over semaglutide and liraglutide in weight reduction and metabolic control. Its dose-dependent effect allows personalized treatment approaches (Ciudin et al., 2024). Despite effectiveness, side effects like nausea and diarrhoea may impact adherence; however, gradual dose escalation can improve tolerance (Stanford et al., 2017). Tirzepatide maintains a safety profile comparable to other agents, offering additional clinical benefits.

Importantly, although pharmacological strategies such as GLP-1 and GIP receptor agonists do not consistently replicate the anti-inflammatory impact of bariatric surgery—particularly with respect to reductions in CRP, TNF- α , and IL-6—they show emerging potential. Their anti-

inflammatory effects appear promising, and early findings suggest a possible indirect influence on MMP activity, mediated by improvements in systemic inflammation, oxidative stress, and metabolic parameters (Mirica et al., 2022; Pan et al., 2024; García-Prieto et al., 2019). However, the current evidence is limited and largely preclinical. Comprehensive mechanistic studies, including in vitro experiments and translational models, are warranted to clarify whether these agents directly modulate MMP expression or activity.

Pharmacological agents thus remain a valuable element of integrated obesity care—especially in patients who cannot undergo surgery or require long-term support after bariatric procedures. They offer substantial benefits in weight loss and glycemic control, though their capacity to comprehensively modulate systemic inflammation, ECM remodeling, and achieve remission of T2DM remains inferior to surgical interventions. Optimizing treatment for obesity will likely require a personalized and combined approach, leveraging the strengths of both pharmacological and surgical modalities.

Intervention	Primary mechanism	Mean total weight loss (TWL)	HbA1c change	Inflammation markers	MMPs – reported effects	Key advantages	Key limitations / AEs	Evidence strength
GLP-1 RA (e.g., semaglutide, liraglutide)	GLP-1 receptor agonism → ↓ appetite, delayed gastric emptying, ↑ insulin, ↓ glucagon	~10–15% (dose-dependent; obesity indications)	~1.0 to 1.8%	↓ CRP, ↓ IL-6 (heterogeneous)	Direct effects on MMPs: insufficient evidence; potential indirect reduction via ↓ inflammation/weight	Substantial WL and glyce mic control; CV benefit (class)	GI AEs (nausea, vomiting), adherence, access/cost	Multiple RCTs, meta-analyses
Dual GLP-1/GIP (tirzepatide)	Dual GLP-1 & GIP agonism → augmented incretin effect	~15–22% (obesity); superior to GLP-1 RA in NMA	~2.0 to 2.5%	↓ CRP (signals), broader metabolic improvements	Direct MMP modulation : unknown; plausible indirect effects via anti-inflammatory/weight pathways	Highest WL among drugs; strong glyce mic effects	GI AEs; titration needed; long-term safety ongoing	Large RCTs (T2D/obesity), network meta-analyses
Post-bariatric adjunct	Anti-obesity meds after	Addit ional 5–10%	Improves glyce	May reinforce ↓ CRP	No direct data on MMPs	Useful for weigh	Evidence heterog	Multicenter cohorts;

pharmacotherapy	surgery for weight regain/adequate loss	TWL possible	metabolic when added			to regain	endogenous; selection bias	limited RCTs
Bariatric surgery (RYGB, SG, etc.)	GI anatomy/hormonal changes → durable WL, metabolic reset	~25–30% durable WL; >50% EWL common	T2D remission up to ~80–90% (select ion-dependent)	Consistent ↓ CRP/hs-CRP, ↓ IL-6/TNF-α, ↓ ferritin/oxidative stress	↓ MMP-9, normalization ↓/↔ MMP-2, ↓ MMP-8 (esp. T2D); heterogeneity by procedure/study	Greater and most durable metabolic benefit; CV risk reduction	Surgical risks; micronutrient deficiency; variability by procedure	RCTs/large cohorts; mechanistic studies on MMPs

6. Limitations and Future Directions

Despite the encouraging findings outlined in this review, several limitations must be acknowledged. First, much of the data is derived from heterogeneous clinical studies with variable methodologies, limiting direct comparisons. Additionally, long-term effects of bariatric surgery on MMP activity remain insufficiently studied, with most research focusing on short- to medium-term outcomes. The impact of pharmacological interventions on MMPs is even less explored, particularly regarding tissue-specific mechanisms and inflammatory resolution. Future studies should aim to clarify these mechanisms through longitudinal and mechanistic trials, and assess whether pharmacological modulation of MMPs could replicate the structural and metabolic improvements seen with surgery.

7. Conclusions

This review summarizes the role of MMPs in obesity, with a particular focus on ECM remodeling and inflammation, particularly their involvement in ECM remodeling, systemic inflammation and metabolic dysfunction.

Consistent evidence demonstrates modulation of MMPs activity after bariatric surgery. The reduction in MMP-9 levels and normalization of MMP-2 activity after bariatric surgery suggest their role in obesity-induced inflammation and metabolic dysfunction. By interfering with pathological ECM remodeling and reducing systemic inflammatory markers such as CRP and pro-inflammatory cytokines (e.g., TNF-α and IL-6), bariatric surgery contributes to reduced cardiovascular risk, improved insulin sensitivity and overall metabolic outcomes. These findings are consistent with the observed decrease in macrophage infiltration and resolution of local adipose tissue inflammation, further supporting the role of MMPs modulation as a key mechanism driving the anti-inflammatory and metabolic benefits of surgical interventions. While drug therapies, an alternative method in weight reduction and glycemic control, provide limited research evidence regarding their effects on MMPs activity and ECM remodeling Comparative analysis confirms the superior long-term efficacy of bariatric surgery on the underlying biochemical processes of obesity, particularly through its systemic effects on inflammation and tissue remodeling. Moreover, the sustained weight loss and improved metabolic health observed during bariatric interventions are key factors in the long-term

resolution of obesity-related pathologies. Pharmacological therapies, while effective in inducing weight loss and improving glycemic parameters, are limited in their ability to replicate the wide-ranging effects of surgery. These findings underscore the need for expanded research on pharmacologic interventions, particularly in the areas of modulation of MMPs activity and inflammation.

There are several limitations inherent in the existing literature. The paucity of studies evaluating the long-term effects of bariatric surgery on MMPs activity limits the ability to draw definitive conclusions about the persistence of these biochemical changes. Variability in surgical techniques and study methodology further complicates the interpretation of results and limits their generalizability. Limited information on the impact of drug treatment in the context of MMPs also points to the limited scope of current research, leaving unanswered critical questions about the full potential of these agents to treat inflammation and tissue dysfunction associated with the pathogenesis of obesity.

The insights gained from this review significantly advance the understanding of the complex biochemical and molecular pathways involved in obesity treatment, particularly the role of MMPs as mediators of inflammation, tissue remodeling and metabolic dysfunction. The findings underscore the potential of bariatric surgery to combat the multifactorial pathology of obesity, offering profound benefits that extend beyond weight loss to include systemic improvements in inflammatory parameters. A comparative analysis of treatment options highlights the strengths and limitations of both surgical and pharmacological approaches, emphasizing the critical importance of personalized and integrative strategies in optimizing outcomes. Reflecting on the challenges and opportunities identified in this work, there is optimism about the future of obesity research and treatment, with interdisciplinary efforts to improve therapeutic options. This work contributes to the scientific dialogue on obesity treatment and affirms the need for continued innovation in addressing this global health challenge.

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