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Research Progress on the Mechanisms of the Effects of Laparoscopic Sleeve Gastrectomy on Free Fatty Acids and Tumor Necrosis Factor in Obese Patients

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Abstract: Laparoscopic sleeve gastrectomy (LSG), as an effective treatment for morbid obesity and its metabolic complications, exerts its therapeutic effects by significantly reducing body weight and improving metabolic disorders. Its core mechanisms involve multi-level regulation of free fatty acid (FFA) metabolism and chronic low-grade inflammatory states (represented by tumor necrosis factor-alpha, TNF-α). This paper systematically reviews the direct impact of LSG on FFA dynamics including lipolysis, tissue uptake, and oxidation, as well as the molecular pathways through which it indirectly regulates TNF-α by reducing adipose tissue inflammation, improving intestinal barrier function, and modulating epigenetic modifications such as SCD gene methylation. Postoperatively, FFA and TNF-α form a bidirectional promoting feedback loop. LSG effectively breaks this vicious cycle of mutual promotion between the two under obese conditions by reducing FFA levels and inhibiting TNF-α expression. Lower FFA levels alleviate inflammatory signal activation, while reduced TNF-α inhibits lipolysis, collectively promoting the restoration of insulin sensitivity. A thorough understanding of these mechanisms provides a theoretical basis for optimizing surgical strategies and developing targeted therapies.

Keywords: Laparoscopic sleeve gastrectomy; Free fatty acids; Tumor necrosis factor; Obesity; Metabolic syndrome

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1. Introduction

Currently, obesity has become a critical health issue in urgent need of resolution within the global public health domain. It is closely associated with various metabolic diseases and significantly increases the risk of cardiovascular diseases, diabetes, and even cancer. A variety of treatment methods for obesity exist, including dietary interventions, pharmacological treatments, and surgical procedures. Among these, LSG as an emerging weight-loss surgery, has garnered widespread attention due to its minimal trauma and rapid recovery.

LSG is not only an effective weight-loss method but has also been found to significantly improve obesity-related metabolic disorders. Studies have shown that metabolic indicators such as blood glucose and blood lipids in patients after surgery have significantly improved, providing strong support for the long-term health of obese patients. Although LSG has demonstrated remarkable efficacy, the specific molecular mechanisms underlying its improvement of metabolism, particularly in regulating the network of free fatty acids (FFA) and tumor necrosis factor-alpha (TNF-α), remain to be thoroughly elucidated. Adipose-related factors play a pivotal role in the metabolic abnormalities and inflammatory responses associated with obesity. In recent years, the impact of LSG on adipose-related factors has become a research hotspot. This article has systematically elaborated on the mechanisms by which LSG affects FFA and TNF-α, using FFA and tumor necrosis factor (TNF-α) as representatives, to provide references for clinical practice and future research and to offer new insights into the treatment of obesity and its comorbidities.

2. The impact of LSG on metabolic indicators

Currently, LSG has become an effective treatment for long-term weight loss maintenance in patients with severe obesity and those who have not achieved satisfactory results with traditional weight loss methods. Within the first year after LSG, patients experience significant weight reduction, losing 65–75% of their body weight and fat mass, which can be sustained over the long term. This is accompanied by a notable decrease in abdominal subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT). Currently, research on the mechanisms underlying the remission of obesity, diabetes, and comorbidities following bariatric surgery primarily focuses on post-operative caloric intake, weight loss, changes in gastrointestinal hormone secretion, and islet cell proliferation. However, no single mechanism has been able to comprehensively and clearly explain the weight loss, glycemic control, metabolic improvements, and subsequent long-term effects.

The weight loss achieved by patients after LSG not only brings about significant changes in body shape but also improves the incidence of obesity-related complications, such as hypertension, diabetes, and hyperlipidemia [1]. Studies have shown that approximately 50–80% of diabetic patients can achieve complete remission after surgery, particularly among those with a higher preoperative BMI and shorter duration of diabetes [2]. Langer et al. discovered a significant decrease in plasma ghrelin levels after bariatric surgery and suggested that the gastrointestinal hormone ghrelin is involved in the mechanisms of reduced food intake and weight loss following sleeve gastrectomy [3]. In terms of improving insulin sensitivity, LSG may achieve this by activating specific signaling pathways. After LSG, the expression levels of proteins related to insulin signal transduction in patients' muscle and adipose tissues significantly increase, indicating that LSG helps enhance the biological effects of insulin. Furthermore, LSG improves metabolism by altering the secretion of intestinal hormones, a process involving increased secretion of intestinal hormones such as GLP-1 and GIP. These hormones play a crucial role in regulating appetite and insulin sensitivity. After LSG, patients' GLP-1 levels significantly rise, which helps improve insulin resistance and reduce appetite [4,5].

Meanwhile, obese patients often suffer from metabolic-associated fatty liver disease (MAFLD), and surgery may also reduce hepatic fat infiltration by improving liver metabolic function. Research has shown that one year after surgery, the proportion of patients with hepatic hyperechogenicity changes, as indicated by liver ultrasound, decreased from 21% before surgery to 1.5%. Furthermore, post-surgical changes were observed in the intestinal microbiota of patients, and these changes were closely related to improvements in metabolic status [6]. These findings indicate that LSG not only aids in weight loss but also effectively improves the overall health of patients. The effects of LSG on post-surgical weight loss, as well as improvements in blood glucose levels, reduction in insulin resistance, lipid disorders, fatty liver, and inflammation, are significant and independent of post-surgical dietary changes, further supporting the potential of LSG in the treatment of metabolic syndrome.

3. Regulatory mechanism of LSG on FFA metabolism

3.1. Changes in FFA levels after LSG

FFAs can exacerbate systemic inflammation by promoting the secretion of pro-inflammatory cytokines from adipocytes. There is a close relationship between the reduction in FFA levels and metabolic improvement. Firstly, a decrease in FFA levels helps reduce insulin resistance and alleviate chronic inflammatory responses. In obese patients, excessive accumulation of FFAs can lead to dysfunction of adipocytes and hepatocytes, thereby reducing insulin sensitivity. Therefore, monitoring the dynamic changes in post-surgical FFA levels is an important area of research for obese patients undergoing LSG. Studies by Campos et al. showed a transient increase in FFA levels 14 days after weight loss surgery, possibly due to a surge in catecholamines caused by surgical stress, which activates hormone-sensitive lipase (HSL) in adipose tissue [7]. However, during the stable post-surgical period, the reduction in FFA levels in the surgical group was twice that of the control group. Research by Farey et al. also demonstrated a significant decrease in FFA levels to below preoperative baseline levels three months after surgery, with a reduction significantly greater than that in the diet intervention-only group [8]. The changes in post-operative FFAs are directly related to the patient's metabolic state and post-operative recovery. Low FFA levels are associated with better glycemic control and a lower incidence of complications. Specifically, the reduction in FFA levels after surgery is believed to result from the redistribution of adipose tissue and improved metabolism. The decrease in adipose tissue directly affects the release and utilization of FFAs, thereby enhancing insulin sensitivity. This indicates the crucial role of FFAs in post-operative metabolic regulation.

Additionally, the dynamic changes in FFAs are also related to the redistribution of adipose tissue. Research has found that after LSG, there is a significant change in the distribution of adipose tissue in patients, particularly a reduction in visceral fat. This change further promotes the metabolism and utilization of FFAs. This process may improve overall metabolic status by influencing the secretory function of adipocytes and the action of insulin. Therefore, the dynamic changes in post-operative FFA levels not only reflect the patient's metabolic state but may also serve as an important biomarker for evaluating surgical outcomes and patient recovery.

3.2. Molecular mechanisms of FFA regulation by LSG

3.2.1. The role of reduced visceral fat

After LSG, patients experience significant decreases in blood glucose, lipid levels, and inflammatory markers. Among these, the reduction in abdominal visceral fat is considered one of the key factors in improving these metabolic indicators. Visceral adipose tissue (VAT) is one of the primary sources of FFA release, and its reduction is a direct cause of the decrease in FFAs. Studies have shown that LSG can significantly reduce the volume and mass of visceral fat, and this reduction in fat is associated with improvements in insulin sensitivity and blood glucose levels. This process is closely related to the metabolic improvements observed after surgery. Additionally, patients experience a decrease in food intake, leading to a significant reduction in fat breakdown and FFA release, particularly resulting in a notable decrease in liver fat content. This also demonstrates the effectiveness of LSG in improving fatty liver [4]. Overall, LSG improves metabolic disorders in obese patients by reducing the volume and mass of visceral fat, thereby decreasing the production and release of FFAs.

3.2.2. Epigenetic regulation: The key role of SCD gene methylation

Stearoyl CoA Desaturase-1 (SCD-1) is a crucial enzyme in the metabolism of free fatty acids (FFAs), catalyzing the conversion of saturated fatty acids (SFAs) to monounsaturated fatty acids (MUFAs). It is considered to play a pivotal role in obesity-related lipid metabolism disorders and insulin resistance. Research by Morcillo, S revealed that DNA methylation levels in the promoter region of the SCD gene were lower in morbidly obese subjects before bariatric surgery but increased to levels similar to those in the control group after the surgery [9]. Changes in DNA methylation genes were associated with alterations in free fatty acid levels and HOMA-IR, suggesting that DNA methylation of the SCD gene promoter is linked to metabolic improvements in morbidly obese patients following bariatric surgery.

3.2.3. Expression of genes related to fatty acid oxidation

Fatty acid oxidation is a critical process in cellular energy metabolism. In the context of obesity, impaired fatty acid oxidation capacity is a significant factor contributing to FFA accumulation and metabolic disorders. LSG exerts a significant regulatory effect on the expression of fatty acid oxidation genes in obese patients. Studies have shown that LSG can upregulate genes related to fatty acid oxidation, thereby enhancing FFA metabolism and clearance. This surgical intervention effectively reduces FFA concentrations in the bloodstream, subsequently lowering obesity-related metabolic risks and improving abnormalities in glucose and lipid metabolism [10].

Firstly, the upregulation of fatty acid oxidation genes in obese patients after LSG may be related to the physiological changes induced by the surgery. Postoperatively, patients experience a reduction in food intake, accompanied by alterations in the body's energy balance. A drastic reduction in adipose tissue promotes the release of fatty acids, which in turn stimulates the expression of genes involved in fatty acid oxidation. Research has shown that after LSG, genes related to fatty acid oxidation in liver and muscle tissues, such as CPT1 (carnitine palmitoyltransferase 1), a rate-limiting enzyme for mitochondrial membrane transport, and ACOX (acyl-CoA oxidase), the first enzyme in peroxisomal β-oxidation, exhibit significant upregulation. The enhanced expression of these genes helps to increase the oxidation rate of fatty acids and reduce the concentration of FFAs in the body, thereby alleviating symptoms associated with metabolic syndrome [11].

Moreover, the improvement in fatty acid metabolism plays a positive role in the clearance of FFAs. FFAs are intermediate products of fat metabolism, and their excessive accumulation is closely linked to various metabolic diseases. Studies have found that after LSG surgery, the concentration of FFAs in patients significantly decreases, which is closely related to the upregulation of fatty acid oxidation genes.

3.2.4. Regulation of endocrine factors

In obese patients, changes in endocrine factors such as myostatin and leptin play a crucial regulatory role in the release and metabolism of FFAs and tumor necrosis factor (TNF-α). Myostatin is a novel muscle-secreted factor that not only plays a role in FFA metabolism but also participates in regulating insulin sensitivity and glucose metabolism. Myostatin enhances the utilization of fatty acids in cells and inhibits the concentration of circulating FFAs. The serum concentration of myostatin in obese patients is significantly lower than that in individuals with normal body weight. However, in patients who have undergone LSG, serum myostatin levels significantly increase, further improving FFA metabolism and thereby helping to alleviate obesity-related metabolic syndrome. This change is not only negatively correlated with body weight, waist circumference, and body mass index (BMI) but also associated with insulin resistance and glycated hemoglobin (HbA1c) levels. Therefore, myostatin may play a significant role in regulating the release and metabolism of FFAs.

Leptin is a hormone secreted by adipose tissue that acts on the hypothalamus to regulate appetite and energy balance. In obese patients, leptin levels are typically high; however, its effects are often accompanied by leptin resistance, which weakens its regulatory role in FFA metabolism. Studies have found that obesity leads to a state of chronic inflammation, and elevated levels of TNF-α, in turn, affect the function of leptin. TNF-α is one of the key factors inducing leptin resistance, as it can inhibit the leptin signaling pathway (such as JAK-STAT), further leading to abnormal release of FFAs [12]. This suggests that the interaction of endocrine factors and their impact on FFA metabolism may be an important mechanism underlying obesity-related metabolic disorders.

4. Regulation network of LSG on tumor necrosis factor-α (TNF-α)

4.1. Changes in TNF-α levels after LSG

Tumor necrosis factor-α (TNF-α), as an important inflammatory marker, its elevation is typically associated with the chronic low-grade inflammatory state related to obesity, a condition considered to be the basis for various metabolic diseases. Studies have shown that the chronic inflammatory state in obese patients is often accompanied by high levels of TNF-α. Six months after LSG, TNF-α levels significantly decrease and are negatively correlated with weight loss; they also show a negative correlation with other inflammatory markers such as C-reactive protein [13]. This improvement not only helps reduce the risk of related complications but may also promote overall metabolic health in obese patients. Maymó-Masip's research indicates that serum TNF-α levels rapidly decline after LSG, with a 17.8% reduction at six months post-surgery, independent of weight loss [14]. One year after surgery, TNF-α mRNA expression in adipose tissue remains continuously suppressed, paralleling improvements in insulin resistance.

4.2. Molecular mechanisms of LSG in regulating TNF-α

4.2.1. Regulation of the sTWEAK-TNF-α antagonistic axis

Soluble TNF-α-like weak inducer of apoptosis (sTWEAK) is a soluble form released extracellularly after membrane-bound TWEAK (mTWEAK) is cleaved by proteases such as ADAMs. In diseases associated with inflammation, the level of sTWEAK decreases. Meanwhile, sTWEAK can hinder the activity of TNF-α in human cells. The study by Maymó-Masip, E revealed that in human adipocytes, sTWEAK downregulates the production of the TNF-α cytokine by obstructing intracellular TNF-α signaling [14]. In patients with severe obesity, the circulating levels of sTWEAK are significantly reduced. The elevation of sTWEAK levels represents a protective mechanism that inhibits the inflammatory effects of TNF-α after LSG. Following bariatric surgery, soluble TWEAK levels increase in 69% of severely obese subjects, blocking the NF-κB inflammatory pathway by inhibiting TNF-α-induced IKB-α phosphorylation and JNK activation. NF-κB is a key transcription factor involved in regulating intracellular inflammatory responses. In obese patients, the activation of NF-κB is often accompanied by an upregulation of TNF-α. After LSG, the reduction in adipose tissue leads to decreased NF-κB activity, which not only helps reduce TNF-α synthesis but also suppresses the production of other inflammatory factors.

4.2.2. Improvement in intestinal barrier function and alleviation of endotoxemia

The human intestine serves as a natural habitat for a diverse array of complex microbial communities and plays a crucial role in maintaining host homeostasis [15]. Obesity is associated with increased intestinal permeability and dysbiosis, leading to the entry of lipopolysaccharide (LPS) into the bloodstream, which activates the TLR4 pathway and promotes TNF-α production. LSG can improve intestinal blood flow redistribution, reduce mucosal permeability, and enhance the composition of the intestinal microbiota. The ratio of Firmicutes to Bacteroidetes can be considered a predictive indicator of intestinal dysbiosis in morbidly obese patients [16]. Postoperatively, the decrease in the Firmicutes/Bacteroidetes ratio and the reduction in LPS-producing bacteria further diminish the activation of the TLR4/NF-κB pathway, thereby inhibiting TNF-α production. Changes in the gut microbiota may be associated with alterations in the expression of related biomarkers after surgery [17,18]. The study by Tabasi, M included 126 patients with morbid obesity who underwent laparoscopic sleeve gastrectomy (LSG). Routine biochemical markers, hormones (insulin, glucagon), and cytokine levels (IL-6, IL-1β, TNF-α, IL-10, TGF-β1) were measured, and the gut microbiota was quantitatively analyzed using real-time fluorescent quantitative PCR (quantitative PCR, qPCR) [19]. All parameters were measured before surgery and at 3 and 12 months postoperatively (designated as F0, F3, and F12, respectively). The results showed elevated levels of *Bacteroidetes*, *Bifidobacterium*, *Akkermansia muciniphila*, *Roseburia*, and *Clostridium* clusters at F3, which were maintained at high levels at F12. Moreover, changes in the microbiota were closely correlated with lipid levels and TNF-α levels.

4.2.3. Regulation of the bile acid-FXR axis

The nuclear receptor Farnesoid X receptor (FXR) plays a crucial role in bile acid homeostasis [20]. After surgery, the bile acid pool typically expands and undergoes compositional changes (with an increased proportion of secondary bile acids), activating intestinal FXR receptors and inhibiting the NF-κB pathway, thereby reducing intestinal epithelial TNF-α expression by 50% [21]. The study by Albaugh, VL demonstrated that bile diversion to the ileum (GB-IL) in a rodent obesity model produced metabolic and satiating effects very similar to those of bariatric surgery [22]. Bile diversion to the ileum improved glucose homeostasis via the intestinal FXR-GLP-1 axis. Changes in the availability of intestinal bile acids, independent of weight loss, suggest that *Akkermansia muciniphila* mediates the metabolic changes observed after bariatric surgery and may have potential applications in the treatment of obesity and diabetes.

5. Interaction between FFAs and TNF-α and regulation by LSG

5.1. Feedback regulation of TNF-α expression by FFAs

FFA (Free Fatty Acids) serve as endogenous ligands for TLR4 (Toll-like Receptor 4) and play a significant role in obese patients, particularly in the context of inflammation and metabolic disorders. FFA are not only substrates for energy metabolism but also function as signaling molecules involved in cellular metabolic regulation. Studies have shown that elevated FFA concentrations lead to the upregulation of TNF-α (Tumor Necrosis Factor-alpha), a process closely associated with chronic low-grade inflammation related to obesity. FFA can promote TNF-α expression by activating the Toll-like receptor 4 (TLR4) pathway, thereby playing a central role in obesity-related inflammatory responses [23,24]. FFA can also enhance TNF-α expression by activating the NF-κB (Nuclear Factor-kappa B) signaling pathway, and TNF-α, in turn, can further induce FFA production, creating a vicious cycle. In this process, high levels of FFA and TNF-α are considered key factors in various pathological conditions, including metabolic syndrome, diabetes, and cardiovascular diseases. LSG can reduce FFA levels, thereby decreasing TLR4/NF-κB pathway activation, further downregulating TNF-α, reversing excessive lipolysis, and establishing a virtuous cycle of metabolic-inflammatory improvement.

Additionally, the chemokine CCL2 (also known as MCP-1, Monocyte Chemoattractant Protein-1) is a crucial regulator of monocyte infiltration into adipose tissue and plays a central role in the pathophysiology of obesity-related inflammation and insulin resistance. Ahmad, R's research indicates that elevated FFA levels in obesity create an environment where TNF-α can trigger CCL2 production through the TLR4/TRIF/IRF3 (Toll-like Receptor 4/TIR-domain-containing adapter-inducing interferon-β/Interferon Regulatory Factor 3) signaling cascade, representing a potential contribution of FFA to metabolic inflammation [25].

5.2. The promoting effect of TNF-α on FFA release

There exists a positive feedback loop between FFA and TNF-α, wherein an increase in FFA levels prompts a rise in TNF-α, and TNF-α, in turn, further enhances FFA release. This mechanism is particularly prominent in obesity and related metabolic syndromes. Chronic inflammatory responses in the obese state led to sustained FFA release, which subsequently exacerbates the expression and secretion of TNF-α. This feedback loop not only affects adipose tissue function but may also result in systemic inflammatory responses, thereby intensifying the occurrence of insulin resistance and other metabolic disorders.

TNF-α exacerbates FFA metabolic disorders through multiple pathways: Firstly, it inhibits insulin signaling. TNF-α can activate inflammation-related signaling pathways such as NF-κB, JNK, and IKKβ in adipocytes, leading to the phosphorylation of IRS1 Ser307, promoting the transcription of inflammatory factors, and hindering their binding to insulin receptors, thereby further suppressing insulin sensitivity [26,27]. In 3T3-L1 adipocytes, JNK and TNF-α can mediate FFA-induced insulin resistance [28]. Secondly, it stimulates lipolysis. The effects of TNF-α are not limited to inhibiting fat synthesis; it also promotes FFA release by activating lipolytic pathways in adipocytes. Specifically, TNF-α can enhance the lipolytic process by activating signaling pathways related to lipolysis, such as the phosphorylation of Hormone-sensitive lipase (HSL). This mechanism is particularly crucial in obese patients, as obesity is often accompanied by a chronic inflammatory state, and the elevation of TNF-α in this state further promotes fat breakdown, leading to increased FFA release. TNF-α promotes lipolysis by activating the key enzyme for fatty acid breakdown, ATGL, and inhibiting the lipid droplet coating protein (Perilipin).

Therefore, TNF-α significantly increases the release of FFAs by inhibiting the activity of fatty acid synthase and promoting lipolysis. This mechanism not only plays a pivotal role in the pathophysiology of obesity but also offers a new perspective for future therapeutic strategies. Interventions targeting TNF-α may become a crucial approach to mitigate FFA release and its associated metabolic disorders.

5.3. Establishment of a metabolic-inflammatory positive feedback loop by LSG

In summary, LSG creates a self-reinforcing improvement by simultaneously intervening in FFA and TNF-α levels (shown in **Figure 1**).

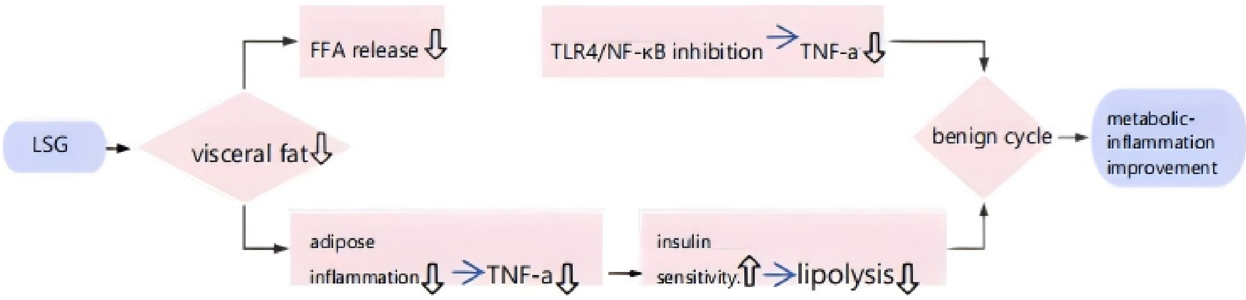

Figure 1. LSG exerts simultaneous effects on FFA and TNF-α levels, leading to a self-reinforcing cycle of improvement.

6. Conclusion

LSG, as an effective treatment for morbid obesity, improves metabolism through multiple interconnected and complementary mechanisms. One of the core aspects involves the simultaneous regulation of FFA metabolism and TNF-α-mediated chronic inflammation, establishing a self-reinforcing positive feedback loop by breaking the vicious cycle between the two. These effects stem from LSG's multidimensional regulation of gastric anatomy, fat distribution, epigenetics, and the microbiota-bile acid axis, independent of mere weight loss.

The elucidation of this mechanistic network not only deepens our understanding of the metabolic benefits of LSG but also holds significant implications for advancing precise interventions in obesity and related metabolic disorders. Future research should further explore the interactions and long-term effects among these mechanisms to drive precise treatment for obesity and related metabolic diseases.

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Disclosure statement

The authors declare no conflict of interest.

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