THE EXPRESSION OF *SFRP5* ON ADIPOSE TISSUES AND ITS ASSOCIATION WITH METABOLIC DISORDERS: A SYSTEMATIC REVIEW

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ABSTRACT

Objectives: This study aims to provide a comprehensive overview of the expression of Secreted Frizzled-related Protein 5 (*Sfrp5*) in adipose tissues and its association with metabolic disorders. **Subjects and Methods:** A systematic review was conducted. PRISMA guidelines and PICOT standards were used in this study. We searched the data using two search databases (PubMed and ScienceDirect). **Results:** Based on two databases, we identified 1853 potentially relevant articles. 10 documents that met all selection criteria were selected. Most articles showed that the expression of *Sfrp5* increased in adipose tissues of mice fed a high-fat diet (HFD) for 8 weeks (n=1), at 16 weeks of mouse age (n=1), and in obese people (n=1). In addition, *Sfrp5* was reported to have the higher expression in the DBA/2J strain (n=1), in the epididymal adipose tissue (n=1), in NASH patients (n=1), and in the presence of PPARγ (n=1). In contrast, some studies have shown that the expression of *Sfrp5* has decreased significantly in the adipose tissue when B6 mice when ingested HFD for 12 weeks (n=1), at 16-31 weeks of mouse age (n=1), and in leptin-deficient mice when eating an HFD until 21-day-year old (n=1). However, a study had shown that the expression of *Sfrp5* decreased when fat accumulation reached a stable level. This study seems to open up an explanation for the inconsistent evidence. These results have highlighted that *Sfrp5* expression strongly correlates with obesity; thus, potential application directions have been shown in treating and preventing obesity (n=4). At the same time, the application potential of sfrp5 in cardiovascular diseases and fatty liver has also been proposed. **Conclusion:** *Sfrp5* is a newly discovered protein in terms of function, so the evidence for *Sfrp5* expression on adipose tissue has many gaps to exploit. Further studies, especially nutritional interventions, need to be carried out to elucidate its potential application to metabolic disorders.

Keywords: *Sfrp5; expression; adipocytes; adipose tissues; metabolic disorders.*

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I. INTRODUCTION

The prevalence of metabolic disorders is increasing dramatically, posing a significant challenge to global health systems.[1] Metabolic disorders have been considered due to disturbances in metabolic processes such as glucose and lipid regulation, which in turn cause redox imbalance leading to cell dysfunction.[2] According to World Health Organization (WHO) data in 2018, obesity caused 2.8 million deaths per year and 35.8 million disability-adjusted life years (DALY).[3] This crisis urgently requires an effective and sustainable solution.

Currently, to find out the molecular mechanisms involved in metabolic disorders, scientists often use biomarkers to measure, quantify, and assess related health and physiology. Therefore, biomarkers have been widely used and valuable in disease. *Sfrp5*, a member of the SFRP family, is a new adipocytokine classified as an anti-inflammatory adipokine. In 2010, Ouchi et

al. showed that the novel anti-inflammatory adipokine *Sfrp5* played a role in inhibiting the pro-inflammatory adipokine.[4] Some studies have subsequently demonstrated that *Sfrp5* was a marker of healthy adipose tissue because its expression has been closely related to fat mass and adipose tissue size.[5] Therefore, *Sfrp5* can become a marker for diagnosing and classifying obesity. At the same time, *Sfrp5* has played an essential role in regulating adipogenesis.[6] From that, scientists became more interested in the S*frp5* to elucidate the mechanism and effects of it on lipid metabolism in the body.

Exploring alterations in the expression of adipose tissue biomarkers under different conditions and their applications has been one of the strategies in treating metabolic disorders worldwide. There have been many studies on the expression of *Sfrp5* in adipose tissue in both humans and laboratory animals,[5,7-9]. However, no systematic review has been conducted to synthesize published research evidence on this issue. To have a comprehensive perspective on *Sfrp5*, we focused on conducting a systematic review of the expression of *Sfrp5* on adipose tissues and its association with metabolic disorders.

II. SUBJECTS AND METHODS

2.1. Research subjects

Publications about the expression of *Sfrp5* on adipose tissues and the association of *Sfrp5* with metabolic disorders were chosen. PICOT standard was used to identify the research subject. *Population:* Published articles; *Intervention:* There was no limitation on study design; it may be an intervention or non-intervention study; *Comparison:* comparison or non-comparison was acceptable; *Outcome:* The expression of *Sfrp5* on adipocytes/adipose tissues; *Time:* There was no limitation on time of the study.

2.2. Research methods

Study design: A systematic review.

Data searching: Two databases were used to search the article: PubMed (https://pubmed.ncbi.nlm.nih.gov/) and Science Direct (https://www.sciencedirect.com/). Keywords used to search: (*Sfrp5*) AND (gene expression) AND ((adipose tissues) OR (adipocytes)) AND (metabolic disorders).

Data abstraction: PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) were followed for the data abstraction process (http://prisma-statement.org/). After searching, Zotero software was used to store the article. Then, all articles were imported into Microsoft Excel, and duplicates were removed. Then, we excluded articles without abstracts and not written in English. Two researchers (HVT, ADN) independently screened potential documents by examining the article titles and abstracts to determine which ones to read thoroughly and which to exclude from the study. If an agreement could not be reached, the ultimate decision was made by a third researcher (DTC). After title screening, the full text of the articles was read and evaluated. Finally, all articles that met the selection criteria based on PICOT were selected.

III. RESULTS

3.1. Searching results

Based on two databases, we identified 1853 potentially relevant articles. After data preprocessing, 709 articles were included in the title screening. The articles with unrelated topics were removed, and 39 were put in the eligibility assessment. Finally, 10 documents that met all selection criteria based on PICOT were selected.

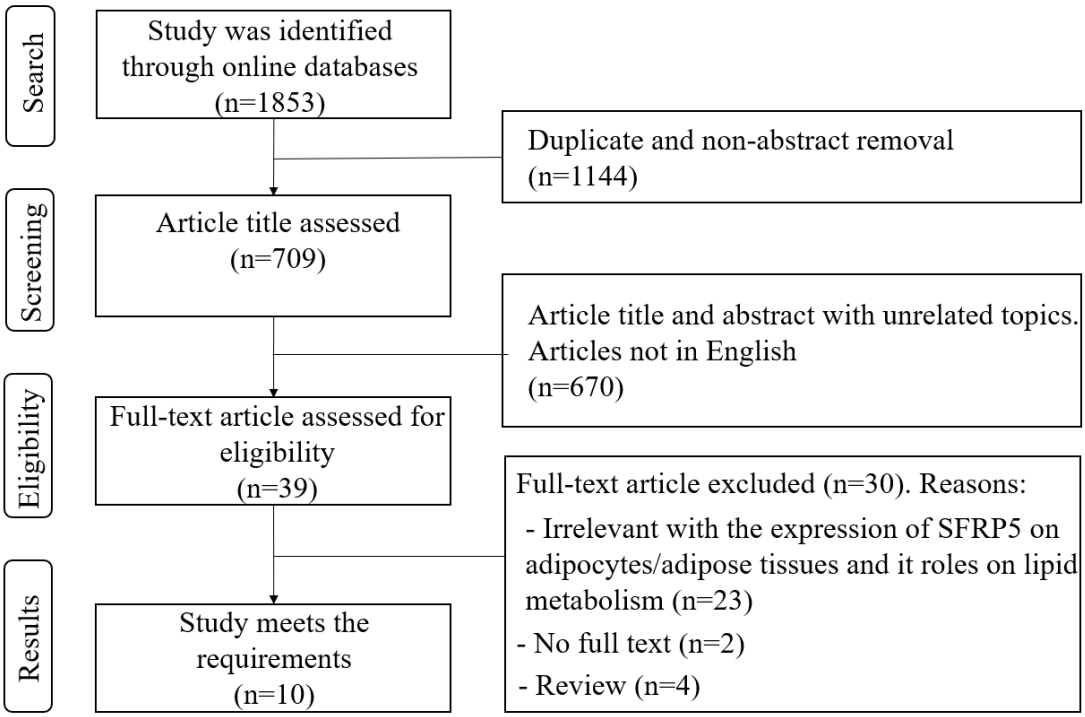

Figure 1. ***PRISMA flow diagram***

3.2. Study characteristics

Characteristics of 10 selected articles have been described in Table 1. The results indicated that there were 02 studies conducted in China,[6,10] in the US,[7,11], Poland,5,12, and Germany.[13,14] The remaining studies were conducted in countries such as Japan,[15], and Spain.[16] The papers have all been published in the last 10 years, from 2012-2022. 07 studies used the intervention study design to compare the expression levels of the *Sfrp5* gene between groups.[5,7,10,11,13,15] Besides, 03 experimental studies have been carried out.[6,14,16]

Table 1. ***Study characteristics***

No	Author	Year	Country	Study design	Main experiment design
1	Schulte et al.[13]	2012	Germany	Intervention study	23 were obese and 12 were normal. The obese group was fed a low-calorie diet for 12 weeks. The degree of *Sfrp5* expression on subcutaneous adipose tissue has been determined.
2	Mori et al.[11]	2012	US	Intervention study	Mice that lost *Sfrp5* gene function were fed 1 in 3 diets: Normal, LFD, HFD. *Sfrp5* expression and adipocyte respiration were evaluated.
3	Koza et al.[7]	2016	US	Intervention study	Male A/J, C57BL/6J, AKR/J, DBA 2J, 129SVImJ, and C57BL/6J mice were fed a HFD for 8 weeks. Body composition and *Sfrp5* expression levels in adipose tissue were evaluated.

No	Author	Year	Country	Study design	Main experiment design
4	Jura et al.[5]	2016	Poland	Intervention study	2 models of obese mice were built: leptin-deficient mice and HFD-fated mice. The level of *Sfrp5* gene expression in subcutaneous adipose tissue before weaning, before adulthood, and during adulthood were assessed.
5	Nakamura et al.[15]	2016	Japan	Intervention study	Mice that lost *Sfrp5* gene function and control mice were used. Mice experienced ischemia and reperfusion. *Sfrp5* gene expression levels were assessed in subcutaneous adipose tissue, epididymis adipose tissue, brown adipose tissue, and cardiac tissue.
6	Chu et al.[12]	2017	Poland	Intervention study	C57BL/6J and 129S1/SvImJ mice were fed HFD and STD from 3 weeks or 8 weeks of age to 31 weeks of age. Sfrp5 gene expression on inguinal, epididymal, and retroperitoneal fat depots were evaluated and compared between groups.
7	Zeng et al.[6]	2018	China	Experimental study	Adipose tissue, kidney tissue, liver tissue were cultured. Cells treated with DMSO, GW9662, PPARγ. *Sfrp5* gene expression was evaluated under various conditions.
8	Zhao et al.[10]	2019	China	Intervention study	Male C57BL/6J mice were fed an STD or HFD for 12 weeks. *Sfrp5* expression was compared in liver, muscle, and adipose tissue.
9	Brandes et al.[14]	2022	Germany	Experimental study	Adipocytes, protocytes and macrophages were isolated in humans. The expression of *Sfrp5* protein levels was evaluated.
10	Bertran et al.[16]	2022	Spain	Experimental study	Subcutaneous fatty tissue and visceral adipose tissue in the obese and normal groups were collected. mRNA expression of *Sfrp5* was evaluated.

3.3. The expression of *Sfrp5* on adipocytes/adipose tissues

The results of *Sfrp5* gene expression were presented in **Figure 2**. The *Sfrp5* gene was reported to increase expression in some cases. Koza et al. showed that the expression of *Sfrp5* in B6 mice had a 20-fold increase when fed an HFD for 8 weeks.[7] Similarly, in Chu's study, *Sfrp5* was significantly elevated at 19 weeks of age when fed an HFD in both B6 and 129S1/SvImJ mice.[12] Also, 02 studies have demonstrated that *Sfrp5* is more strongly expressed in the visceral fat of the obese group than in the regular group in humans[16] and mice.[5] However, the expression of the *Sfrp5* gene also varies among mouse strains, in which the expression of DBA/2J is 20 times higher than that of B6 mice and 2 times higher than that of all other mouse breeds.[7] Epididymal adipose tissue had the highest expression of *Sfrp5*.[15] Expression of *Sfrp5* is significantly increased in the presence of PPARγ, a receptor in the body cells responsible for regulating lipid metabolism.[6]

On the other hand, 03 studies have shown

that the expression of the *Sfrp5* gene was reduced in some cases; for instance, mice were fed an HFD diet for 12 weeks[10], at 31 weeks of age,[12] and in leptin-deficient mice suckling the milk of HFD-fed mothers.[5] The mRNA expression of the *Sfrp5* gene decreased remarkably when fat accumulation gained a stable level.[10] Besides, another study indicated that the expression of the *Sfrp5* gene was attenuated in the presence of GW9662, a PPARγ inhibitor.[6]

Three previous studies have also displayed whether or not the Sfrp5 gene was expressed in some circumstances. *Sfrp5* was expressed in the cytoplasm of mature adipocytes, and this expression does not differ between subcutaneous and visceral adipose tissue.[13,14] Brandes et al. have shown that the *Sfrp5* gene was not expressed in pre-adipocytes and macrophages.

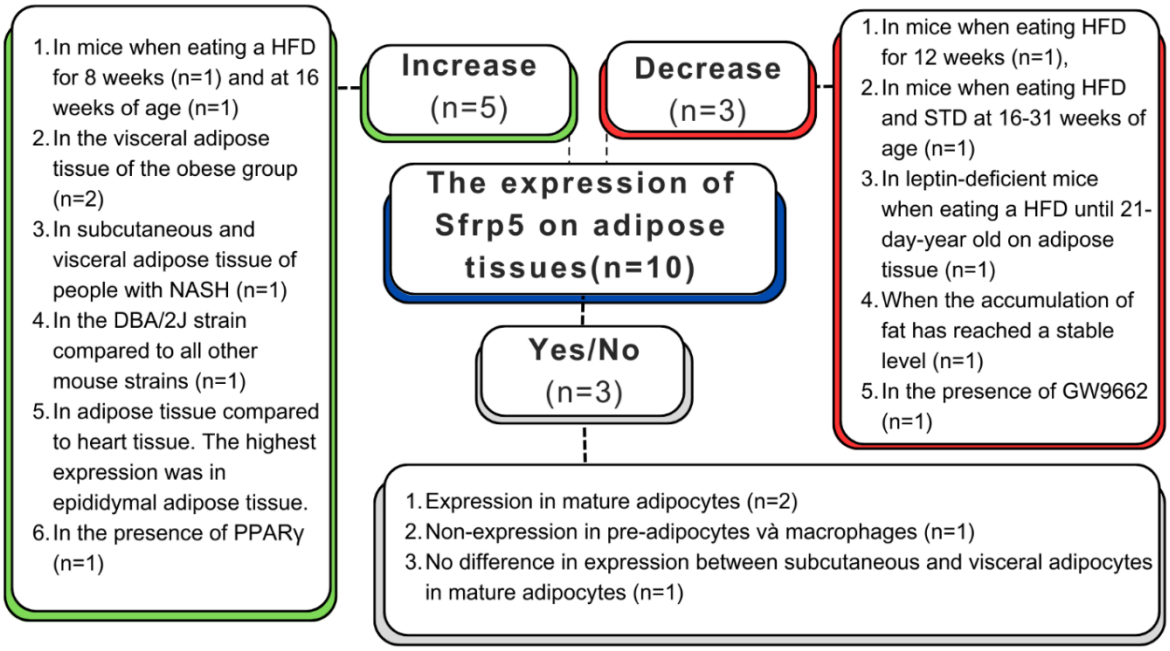

Figure 2. ***The expression of Sfrp5 on adipose tissues***

3.4. Association of *Sfrp5* with metabolic disorders and potential application

According to the study results, the relationship between several metabolic diseases and *Sfrp5* gene expression in adipose tissue has been shown in **Figure 3**, in which the most prominent are obesity (n=4), liver steatosis (n=2), and cardiovascular diseases (n=1).

A low-calorie diet is associated with the *Sfrp5/Wnt5a* pathway.[13,16] These results suggest a new way to treat obesity through nutritional therapies. Furthermore, Mori et al. have intimated that mice with loss of *Sfrp5* gene function resist obesity by increasing mitochondrial oxidative phosphorylation in adipocytes.[11] On the other hand, in the study by Jura and colleagues, the *Sfrp5* gene is reportedly involved in fat deposition.[5] By analyzing the expression of the *Sfrp5* gene, we can better understand the mechanism of fat storage and regulation in the body.

The *Sfrp5/Wnt5a* pathway in adipose tissue has also been shown to play an essential role in liver steatosis disease.[16] Besides, Zhao et al. demonstrated that *Sfrp5*

was associated with liver steatosis through the protein Slurp1. It can reduce the accumulation of triglycerides in the liver by promoting the expression of the *Sfrp5* gene.[10] This appears to be a potential application in developing new therapies for liver steatosis.

In Nakamura's study, *Sfrp5* was shown to have the ability to limit the size of the infarct area in the heart after ischemic reperfusion injury.[15] From these results, *Sfrp5* is suggested to act as a cardioprotective adipokine.

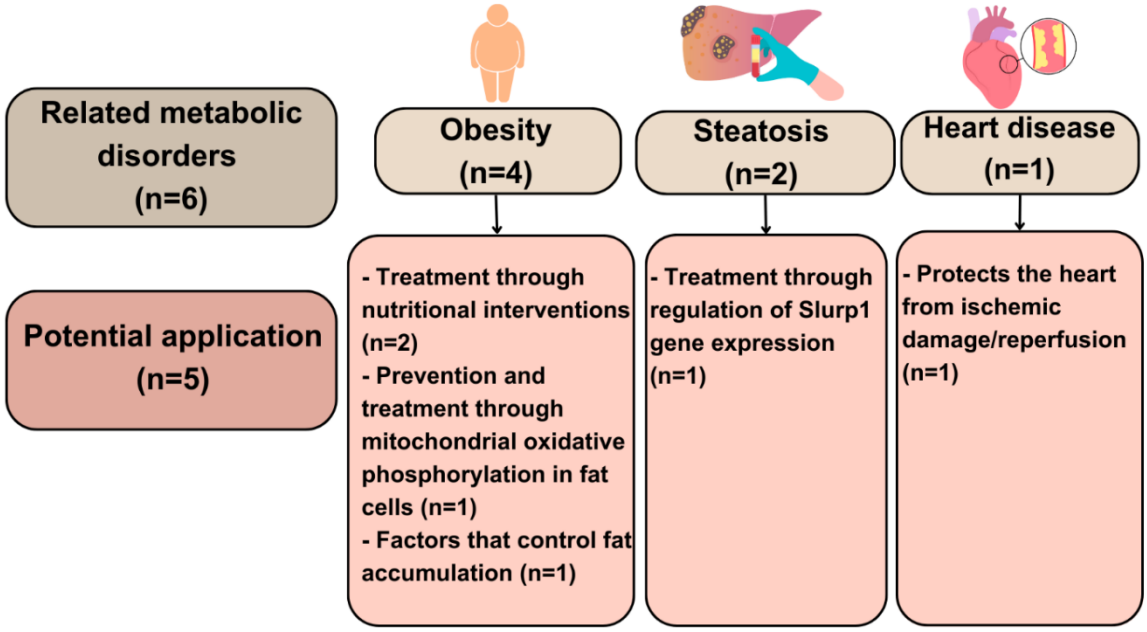

Figure 3. ***Association of Sfrp5 with metabolic disorders and potential application***

IV. DISCUSSION

Almost all reports we collected found that the expression level of *Sfrp5* was significantly lower in hypertrophic adipocytes. It can be explained through the inhibitory interaction between *Sfrp5* and Wnt. Reduced expression of *Sfrp5* activates Wnt signaling and leads to pro-inflammatory status in visceral adipose tissue, promoting the progression of obesity-related diseases.[17] In obese patients, plasma *Sfrp5* was notably minor than in normal people.[18] The study also demonstrated that *Sfrp5* was remarkably reduced in the adipose tissue of obese patients, and its expression was increased when the patients were on a calorie-restricted diet. As a result, *Sfrp5* may be the gene that performs an essential role in protecting the body against the creation of large fat cells and obesity. A study in rats induced with HFD showed a positive effect of *Sfrp5* in the control of hepatic adipogenesis. Specifically, *Sfrp5* was reported to reduce triglyceride synthesis and significantly inhibit *VLDL-TG* secretion through decreased expression of protein expression of fatty acid synthase and stearoyl CoA desaturase-1.[19] A cross-sectional study of obese women also showed similar results when *Sfrp5* levels in visceral fat and subcutaneous adipose tissue were subordinate to those in obese women.[20]

In recent studies, *Sfrp5* is considered one of the potential objects for medical application. From the understanding of *Sfrp5*, many studies have suggested *Sfrp5* as a biomarker for early identification and diagnosis of obesity or metabolic disorders.[21] Animal studies have shown the positive effects of *Sfrp5* in promoting IR, suggesting that *Sfrp5* may also be a mark for treating insulin resistance in obese victims with type 2 diabetes.[19] Based on serum *Sfrp5* levels, doctors can predict coronary artery disease. According to the study, low serum *Sfrp5* levels are a signal of patients with coronary artery disease, and serum *Sfrp5* levels are inversely proportional to the presence and complexity of the disease. Notably, *Sfrp5* is also of interest as a signal and target with great potential for cancer. *Sfrp5* has a crucial function in tumor cell development and invasion; the overexpression of this protein contributes to the reduction of metastasis and prevents the growth of cancer. This study opens up the prospect of *Sfrp5* as a bright object for the therapy of human malignancies. In summary, *Sfrp5* is a newly discovered protein functionally; thus, there has not been much research on its mechanism of action, and there is still a lot of potential to be exploited in the diagnosis and treatment of diseases**.**

However, this research still has some limitations. First, the studies on *Sfrp5* in different subjects and different methods, so the study results may be different, even contradictory, and confuse subsequent studies. Therefore, more large-scale human studies are needed to clearly define the function of *Sfrp5* in metabolic and metabolic disorders. Secondly, although *Sfrp5* is implicated as an adipokine involved in metabolism in many processes, such as inflammation, insulin resistance (IR), and dyslipidemia, its exact contribution and mechanism in humans are still unclear.

V. CONCLUSION

A systematic review was conducted to have a comprehensive perspective on the expression of *Sfrp5* in adipose tissues and its association with metabolic disorders. 10 documents met all the criteria and were chosen. Most of them showed that the expression of *Sfrp5* increased in adipose tissues of mice fed an HFD and in obese people. However, the expression of *Sfrp5* decreased when fat accumulation reached a stable level. The expression of *Sfrp5* varied significantly between mouse strains and adipose tissues. Obesity, fatty liver, and cardiovascular diseases are associated with metabolic disorders closely related to the expression of *Sfrp5*. Potential applications for prevention and treatment have been suggested. Further studies are encouraged to shed light on the inconsistent evidence.

VI. ACKNOWLEDGEMENTS

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VII. AUTHORS' CONTRIBUTIONS

The development of this work originated from DTC. VTH, TTT, and DTC conceptualized the idea. HVT and DTC performed the literature search and data analysis. All authors contributed to writing the initial draft. VTH and DTC reviewed and edited the draft.

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