

## Assessment of Serum SFRP-4 Levels in Subjects with Metabolic Syndrome

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### Abstract

**Background:** Metabolic syndrome is characterized by the clustering of obesity, dysglycaemia, dyslipidaemia, and hypertension, increasing the risk of diabetes and cardiovascular disease. Secreted frizzled-related protein-4 (SFRP-4), a regulator of Wnt signalling, has emerged as a potential marker of metabolic dysfunction.

**Aims:** To assess serum SFRP-4 levels among subjects with metabolic syndrome and determine their association with selected anthropometric, clinical, and biochemical parameters.

**Materials and Methods:** A hospital-based cross-sectional observational study was conducted among 110 subjects with metabolic syndrome at the Department of Biochemistry, ASJSATDS Medical College, Fatehpur, over one year (Jan-Dec, 2024). Anthropometric, clinical, and biochemical parameters were recorded, and serum SFRP-4 levels were assessed.

**Results:** Among 110 subjects, 63 (57.3%) were males and 47 (42.7%) females. Increased waist circumference was present in 89 (80.9%), hypertension in 67 (60.9%), and low HDL-C in 72 (65.5%). Mean SFRP-4 increased with BMI from  $6.82 \pm 1.41$  to  $9.21 \pm 2.03$  ng/mL ( $p=0.004$ ). Levels were higher with fasting glucose  $\geq 126$  mg/dL ( $9.18 \pm 1.94$  vs.  $6.71 \pm 1.35$  ng/mL;  $p<0.001$ ), triglycerides  $\geq 150$  mg/dL ( $8.72 \pm 1.91$  vs.  $7.02 \pm 1.47$  ng/mL;  $p=0.001$ ), low HDL-C ( $8.79 \pm 1.94$  vs.  $7.36 \pm 1.52$  ng/mL;  $p=0.002$ ), and hypertension ( $8.73 \pm 1.91$  vs.  $7.48 \pm 1.62$  ng/mL;  $p=0.003$ ). SFRP-4 correlated positively with BMI ( $r=0.356$ ), waist circumference ( $r=0.391$ ), fasting glucose ( $r=0.428$ ), HbA1c ( $r=0.402$ ), triglycerides ( $r=0.318$ ), and systolic BP ( $r=0.271$ ), while HDL-C showed an inverse correlation ( $r=-0.286$ ); all  $p<0.05$ .

**Conclusion:** Higher serum SFRP-4 levels were associated with multiple metabolic abnormalities, suggesting its potential as a biomarker of metabolic dysfunction in metabolic syndrome.

**Keywords:** SFRP-4; Metabolic Syndrome; Insulin Resistance; Obesity; Dyslipidaemia; Dysglycaemia.

## Introduction

Metabolic syndrome (MetS) is a multifactorial metabolic disorder characterized by the clustering of central obesity, impaired glucose regulation, hypertension, and atherogenic dyslipidemia [1]. Its growing prevalence has made it an important public health concern because affected individuals have substantially increased risks of type 2 diabetes mellitus (T2DM), cardiovascular disease, and other metabolic complications [2]. The pathophysiology of MetS involves complex interactions between adipose tissue dysfunction, insulin resistance, chronic low-grade inflammation, and disturbances in lipid and glucose metabolism. Therefore, identification of novel biochemical markers that reflect early metabolic alterations may improve risk assessment and facilitate timely intervention. Secreted frizzled-related protein 4 (SFRP4) is a member of the secreted frizzled-related protein family and functions as an extracellular modulator of Wnt signalling, a pathway involved in adipogenesis, glucose metabolism, and cellular differentiation [3]. Increasing evidence suggests that SFRP4 is closely associated with adipose tissue dysfunction and metabolic abnormalities. Experimental studies have demonstrated that altered SFRP4 expression can influence adipocyte differentiation and adipokine secretion, thereby potentially contributing to disturbances in glucose metabolism and insulin sensitivity [4]. Clinical investigations have further reported increased circulating SFRP4 concentrations in individuals with T2DM compared with normoglycaemic subjects, supporting its potential relevance as a metabolic biomarker [5]. SFRP4 has also been associated with obesity and insulin resistance, mechanisms that are central to the development and progression of MetS [6]. More recently, higher serum SFRP4 concentrations have been observed in individuals with prediabetes and T2DM and shown to correlate with HbA1c, HOMA-IR, and inflammatory markers, suggesting that SFRP4 may reflect early metabolic and inflammatory disturbances [7].

The present study aims to assess serum SFRP-4 levels among subjects with metabolic syndrome and to explore its potential association with the metabolic abnormalities that characterize the condition. The study also seeks to determine whether SFRP-4 levels differ according to selected clinical and biochemical parameters, thereby evaluating its possible usefulness as a biomarker for identifying and understanding metabolic dysfunction in affected individuals.

## Materials and Methods

**Study design:** A hospital-based cross-sectional observational study was conducted among 110 subjects with metabolic syndrome at the Department of Biochemistry, Amar Shaheed Jodha Singh Ataiya Thakur Dariyao Singh Medical College Fatehpur, Uttar Pradesh, India, over a period of one year (Jan-Dec, 2024). Eligible participants were recruited consecutively during the study period until the required sample size was achieved.

### Inclusion criteria:

- Subjects fulfilling the diagnostic criteria for metabolic syndrome.
- Subjects willing to participate in the study and provide informed consent.

### Exclusion criteria:

- Subjects with acute or chronic inflammatory or infectious diseases.
- Subjects with known malignancy or severe systemic illness.
- Pregnant women.
- Subjects unwilling to participate in the study or provide informed consent.

## Sample collection and serum SFRP-4 estimation:

Blood samples were collected from the study participants using standard aseptic procedures. Serum was separated by centrifugation, and serum secreted frizzled-related protein-4 (SFRP-4) levels were estimated using the laboratory procedures followed during the study. Laboratory quality control was performed according to the established laboratory protocols.

### Statistical Analysis

Data were analysed using appropriate descriptive and inferential statistical methods. Continuous variables were expressed as mean  $\pm$  standard deviation (SD), while categorical variables were presented as frequencies and percentages. Comparisons of categorical variables were performed using the Chi-square test or Fisher's exact test, as appropriate. Differences in mean SFRP-4 levels across

groups were assessed using the independent-samples *t*-test or one-way analysis of variance (ANOVA), as applicable. Pearson's correlation analysis was used to evaluate the relationship between serum SFRP-4 levels and selected anthropometric, clinical, and biochemical parameters. A two-tailed *p*-value  $<0.05$  was considered statistically significant.

### Result

**Table 1.** Distribution of study subjects according to age and sex

| Variable    | Category  | Number (n=110) | Percentage (%) | p-value |
|-------------|-----------|----------------|----------------|---------|
| Age (years) | <40       | 12             | 10.9           | 0.018   |
|             | 40–49     | 28             | 25.5           |         |
|             | 50–59     | 34             | 30.9           |         |
|             | 60–69     | 25             | 22.7           |         |
|             | $\geq 70$ | 11             | 10             |         |
| Sex         | Male      | 63             | 57.3           | 0.118   |
|             | Female    | 47             | 42.7           |         |
| Total       |           | 110            | 100            |         |

The study included 110 subjects with metabolic syndrome. The largest proportion belonged to the 50–59-year age group (34, 30.9%), followed by 40–49 years (28, 25.5%) and 60–69 years (25, 22.7%). Subjects aged  $<40$  years and  $\geq 70$  years accounted for 10.9% and 10.0%, respectively, with the age distribution showing a statistically significant difference ( $p=0.018$ ). Males constituted 63 (57.3%) of the study population, while females accounted for 47 (42.7%); however, the difference in sex distribution was not statistically significant ( $p=0.118$ ).

**Table 2.** Anthropometric and clinical characteristics of study subjects

| Parameter                      | Category  | Number (n=110) | Percentage (%) | p-value  |
|--------------------------------|-----------|----------------|----------------|----------|
| BMI ( $\text{kg}/\text{m}^2$ ) | $<25$     | 18             | 16.4           | 0.006    |
|                                | 25–29.9   | 49             | 44.5           |          |
|                                | $\geq 30$ | 43             | 39.1           |          |
| Waist circumference            | Normal    | 21             | 19.1           | $<0.001$ |
|                                | Increased | 89             | 80.9           |          |
| Hypertension                   | Present   | 67             | 60.9           | 0.021    |
|                                | Absent    | 43             | 39.1           |          |
| Family history of diabetes     | Present   | 58             | 52.7           | 0.034    |
|                                | Absent    | 52             | 47.3           |          |

Regarding anthropometric and clinical characteristics, 49 (44.5%) subjects had a BMI of 25–29.9  $\text{kg}/\text{m}^2$ , while 43 (39.1%) were obese with a BMI  $\geq 30$   $\text{kg}/\text{m}^2$  and only 18 (16.4%) had a BMI  $<25$   $\text{kg}/\text{m}^2$ . The BMI distribution was statistically significant ( $p=0.006$ ). Increased waist circumference was observed in 89 (80.9%) subjects compared with 21 (19.1%) having normal waist circumference ( $p<0.001$ ). Hypertension was present in 67 (60.9%) subjects, whereas 43 (39.1%) were normotensive, showing a significant difference ( $p=0.021$ ). A family history of diabetes was reported by 58 (52.7%) subjects and was absent in 52 (47.3%), with this difference also being statistically significant ( $p=0.034$ ).

**Table 3.** Biochemical profile of study subjects

| Biochemical parameter                           | Category   | Number (n=110) | Percentage (%) | p-value  |
|-------------------------------------------------|------------|----------------|----------------|----------|
| Fasting blood glucose ( $\text{mg}/\text{dL}$ ) | $<100$     | 19             | 17.3           | $<0.001$ |
|                                                 | 100–125    | 47             | 42.7           |          |
|                                                 | $\geq 126$ | 44             | 40             |          |

|                       |         |    |      |        |
|-----------------------|---------|----|------|--------|
| Triglycerides (mg/dL) | <150    | 24 | 21.8 | <0.001 |
|                       | 150–199 | 42 | 38.2 |        |
|                       | ≥200    | 44 | 40   |        |
| HDL-C (mg/dL)         | Normal  | 38 | 34.5 | 0.003  |
|                       | Low     | 72 | 65.5 |        |
| HbA1c (%)             | <5.7    | 16 | 14.5 | <0.001 |
|                       | 5.7–6.4 | 43 | 39.1 |        |
|                       | ≥6.5    | 51 | 46.4 |        |

The biochemical profile demonstrated substantial metabolic abnormalities among the study participants. Fasting blood glucose was ≥126 mg/dL in 44 (40.0%) subjects, 100–125 mg/dL in 47 (42.7%), and <100 mg/dL in 19 (17.3%), with a highly significant distribution ( $p<0.001$ ). Triglyceride levels were ≥200 mg/dL in 44 (40.0%) subjects, 150–199 mg/dL in 42 (38.2%), and <150 mg/dL in 24 (21.8%) ( $p<0.001$ ). Low HDL-C was present in 72 (65.5%) subjects, compared with 38 (34.5%) having normal HDL-C levels ( $p=0.003$ ). Similarly, HbA1c was ≥6.5% in 51 (46.4%) subjects, 5.7–6.4% in 43 (39.1%), and <5.7% in 16 (14.5%), demonstrating a statistically significant distribution ( $p<0.001$ ).

**Table 4.** Comparison of serum SFRP-4 levels according to metabolic parameters

| Variable              | Category      | n  | SFRP-4 level (ng/mL),<br>Mean ± SD | p-value |
|-----------------------|---------------|----|------------------------------------|---------|
| BMI                   | <25           | 18 | 6.82 ± 1.41                        | 0.004   |
|                       | 25–29.9       | 49 | 8.14 ± 1.76                        |         |
|                       | ≥30           | 43 | 9.21 ± 2.03                        |         |
| Fasting blood glucose | <100 mg/dL    | 19 | 6.71 ± 1.35                        | <0.001  |
|                       | 100–125 mg/dL | 47 | 8.12 ± 1.69                        |         |
|                       | ≥126 mg/dL    | 44 | 9.18 ± 1.94                        |         |
| Triglycerides         | <150 mg/dL    | 24 | 7.02 ± 1.47                        | 0.001   |
|                       | ≥150 mg/dL    | 86 | 8.72 ± 1.91                        |         |
| HDL-C                 | Normal        | 38 | 7.36 ± 1.52                        | 0.002   |
|                       | Low           | 72 | 8.79 ± 1.94                        |         |
| Hypertension          | Present       | 67 | 8.73 ± 1.91                        | 0.003   |
|                       | Absent        | 43 | 7.48 ± 1.62                        |         |

Serum SFRP-4 levels showed a clear association with several metabolic parameters. Mean SFRP-4 increased progressively with BMI, from 6.82 ± 1.41 ng/mL among subjects with BMI <25 kg/m<sup>2</sup> to 8.14 ± 1.76 ng/mL in those with BMI 25–29.9 kg/m<sup>2</sup> and 9.21 ± 2.03 ng/mL among obese subjects ( $p=0.004$ ). Similarly, SFRP-4 levels increased with fasting blood glucose, reaching 9.18 ± 1.94 ng/mL in subjects with glucose ≥126 mg/dL compared with 6.71 ± 1.35 ng/mL among those with glucose <100 mg/dL ( $p<0.001$ ). Subjects with triglycerides ≥150 mg/dL had significantly higher SFRP-4 levels than those with triglycerides <150 mg/dL (8.72 ± 1.91 vs. 7.02 ± 1.47 ng/mL;  $p=0.001$ ). Low HDL-C and hypertension were also associated with higher SFRP-4 concentrations (8.79 ± 1.94 vs. 7.36 ± 1.52 ng/mL,  $p=0.002$ ; and 8.73 ± 1.91 vs. 7.48 ± 1.62 ng/mL,  $p=0.003$ , respectively).

**Table 5.** Correlation of serum SFRP-4 levels with selected metabolic parameters

| Parameter             | Correlation coefficient<br>(r) | p-value |
|-----------------------|--------------------------------|---------|
| Age                   | 0.214                          | 0.025   |
| BMI                   | 0.356                          | <0.001  |
| Waist circumference   | 0.391                          | <0.001  |
| Fasting blood glucose | 0.428                          | <0.001  |
| HbA1c                 | 0.402                          | <0.001  |
| Triglycerides         | 0.318                          | 0.001   |
| HDL-C                 | –0.286                         | 0.002   |
| Systolic BP           | 0.271                          | 0.004   |

Correlation analysis demonstrated that serum SFRP-4 was positively correlated with several metabolic and clinical parameters. Significant positive correlations were observed with age ( $r=0.214$ ,  $p=0.025$ ), BMI ( $r=0.356$ ,  $p<0.001$ ), waist circumference ( $r=0.391$ ,  $p<0.001$ ), fasting blood glucose

( $r=0.428$ ,  $p<0.001$ ), HbA1c ( $r=0.402$ ,  $p<0.001$ ), triglycerides ( $r=0.318$ ,  $p=0.001$ ), and systolic blood pressure ( $r=0.271$ ,  $p=0.004$ ). In contrast, HDL-C demonstrated a significant inverse correlation with SFRP-4 ( $r=-0.286$ ,  $p=0.002$ ). Overall, the findings suggest that higher SFRP-4 concentrations were associated with greater obesity, dysglycaemia, hypertriglyceridaemia, hypertension, and lower HDL-C, supporting a potential relationship between SFRP-4 and the metabolic abnormalities characteristic of metabolic syndrome.

**Figure: 1.** Distribution of Biochemical Parameters

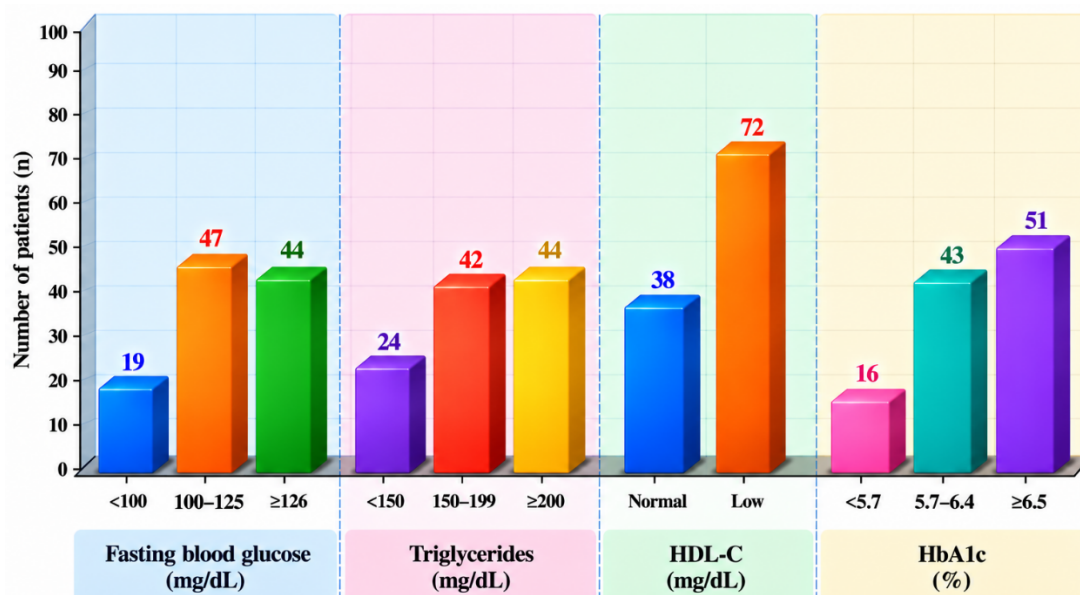
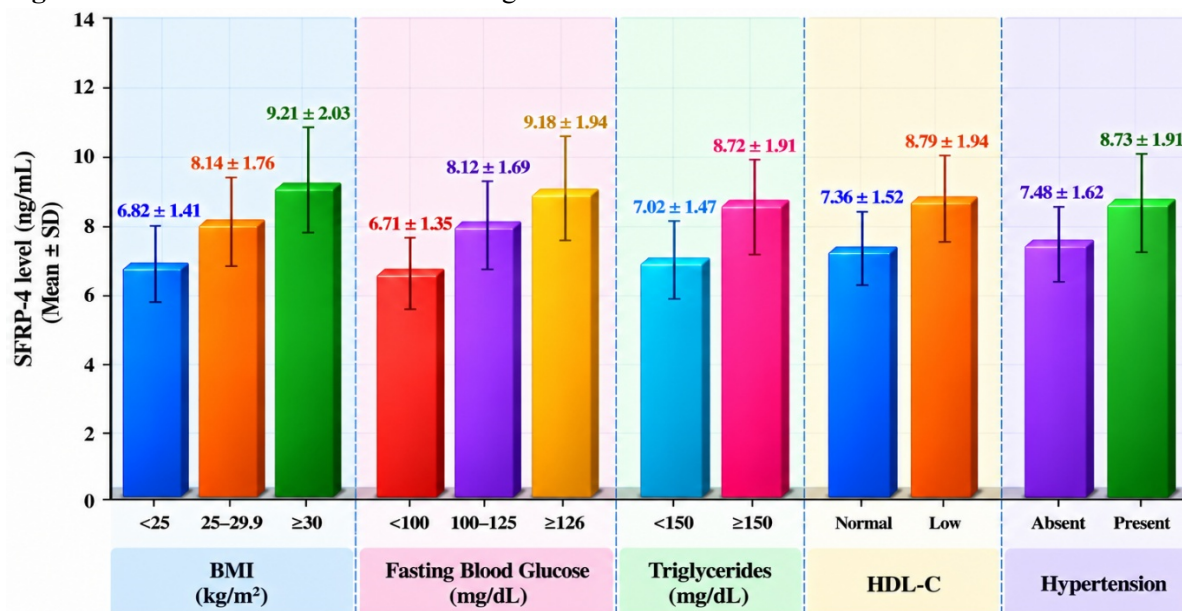


**Figure: 2.** Mean SFRP-4 Levels According to Clinical and Biochemical Parameters



## Discussion

In the present study, the largest proportion of participants with metabolic syndrome was in the 50–59-year age group (30.9%), followed by 40–49 years (25.5%) and 60–69 years (22.7%). The predominance of middle-aged and older adults is

consistent with the progressive accumulation of metabolic risk factors with increasing age. The male predominance observed in the present cohort (57.3%) may reflect the characteristics of the study population rather than a true sex-specific difference, particularly as the difference

was not statistically significant ( $p=0.118$ ). Metabolic syndrome is strongly influenced by age-related changes in body composition, insulin sensitivity and adipose-tissue function, making middle age an important period for the development of clustered metabolic abnormalities [8,9].

Anthropometric findings showed that 83.6% of participants had a BMI  $\geq 25$  kg/m<sup>2</sup>, while increased waist circumference was present in 80.9%. The significant distribution of BMI ( $p=0.006$ ) and the high frequency of central adiposity ( $p<0.001$ ) are important because excess and dysfunctional adipose tissue are closely linked to insulin resistance and chronic metabolic inflammation. Ahmed et al. described dysfunctional adipose tissue as an important contributor to systemic inflammation and insulin resistance through increased free-fatty-acid release and inflammatory signalling [9]. Similarly, reviews of adipose-tissue biology have emphasized that adipose accumulation and altered adipocyte function play a central role in intermediary metabolic disturbances [10]. These observations provide a biological basis for examining adipokine-related molecules such as SFRP-4 in metabolic syndrome.

Hypertension was present in 60.9% of subjects, while 52.7% reported a family history of diabetes. The coexistence of hypertension with obesity and dysglycaemia illustrates the clustering of cardiovascular and metabolic risk factors that characterizes metabolic syndrome. Chronic adipose-tissue inflammation, altered lipid metabolism and impaired insulin signalling can contribute simultaneously to abnormal glucose regulation and cardiovascular risk [9,10]. Thus, the clinical profile observed in this cohort is compatible with the broader metabolic phenotype expected among individuals with metabolic syndrome.

A major finding of the present study was the progressive increase in serum SFRP-4 with increasing BMI. Mean SFRP-4 concentrations increased from  $6.82 \pm 1.41$  ng/mL in subjects with BMI  $<25$  kg/m<sup>2</sup> to  $9.21 \pm 2.03$  ng/mL among those with BMI  $\geq 30$  kg/m<sup>2</sup> ( $p=0.004$ ). This finding is in agreement with Sánchez-Pozos

et al., who reported a positive correlation between SFRP-4 and BMI in individuals with prediabetes and T2DM; the association remained significant after adjustment for age, sex and BMI-related factors [8]. Earlier experimental and clinical work has also linked increased SFRP-4 expression with adipose-tissue dysfunction and impaired insulin sensitivity [3,4]. The present findings therefore support the possibility that higher circulating SFRP-4 accompanies increasing adiposity and may reflect metabolic alterations occurring within dysfunctional adipose tissue.

SFRP-4 was also significantly higher among participants with elevated fasting blood glucose. Subjects with glucose  $\geq 126$  mg/dL had a mean SFRP-4 concentration of  $9.18 \pm 1.94$  ng/mL compared with  $6.71 \pm 1.35$  ng/mL in those with glucose  $<100$  mg/dL ( $p<0.001$ ). This observation is consistent with the findings of Sánchez-Pozos et al., who demonstrated higher SFRP-4 concentrations in prediabetes and T2DM and reported positive associations with HbA1c and HOMA-IR [8]. In addition, previous clinical research has identified SFRP-4 as a potential marker of  $\beta$ -cell dysfunction and insulin resistance, suggesting that increased SFRP-4 may occur alongside deterioration in glucose homeostasis [11]. These findings strengthen the biological plausibility of the present association between SFRP-4 and dysglycaemia.

The present study further demonstrated significantly higher SFRP-4 concentrations in participants with elevated triglycerides ( $8.72 \pm 1.91$  vs.  $7.02 \pm 1.47$  ng/mL;  $p=0.001$ ) and in those with low HDL-C ( $8.79 \pm 1.94$  vs.  $7.36 \pm 1.52$  ng/mL;  $p=0.002$ ). The positive relationship between SFRP-4 and triglycerides is particularly consistent with the findings of Sánchez-Pozos et al., who reported a significant positive correlation between circulating SFRP-4 and triglyceride concentrations [8]. The association with an adverse lipid profile may be explained by the broader relationship between adipose dysfunction, insulin resistance and altered hepatic lipid handling. Experimental evidence suggests that SFRP-4 can interfere with hepatic

insulin signalling and promote lipid synthesis, providing a possible mechanistic link between elevated SFRP-4 and dyslipidaemia [12].

Participants with hypertension also had significantly higher SFRP-4 levels than those without hypertension ( $8.73 \pm 1.91$  vs.  $7.48 \pm 1.62$  ng/mL;  $p=0.003$ ). Although SFRP-4 is not yet established as a specific marker of hypertension, this finding may reflect its relationship with the broader metabolic and inflammatory environment accompanying cardiometabolic disease. SFRP proteins have been increasingly investigated in metabolic and cardiovascular disorders because Wnt-related signalling participates in adipocyte biology, vascular function and metabolic regulation [3]. Therefore, the higher SFRP-4 concentration observed in hypertensive subjects may represent an indirect association with the overall severity of metabolic dysfunction rather than a direct causal relationship.

Correlation analysis provided further support for these findings. SFRP-4 showed significant positive correlations with BMI ( $r=0.356$ ,  $p<0.001$ ), waist circumference ( $r=0.391$ ,  $p<0.001$ ), fasting blood glucose ( $r=0.428$ ,  $p<0.001$ ), HbA1c ( $r=0.402$ ,  $p<0.001$ ), triglycerides ( $r=0.318$ ,  $p=0.001$ ), age ( $r=0.214$ ,  $p=0.025$ ), and systolic blood pressure ( $r=0.271$ ,  $p=0.004$ ). Conversely, HDL-C showed a significant inverse correlation ( $r=-0.286$ ,  $p=0.002$ ). The strongest association in the present analysis was with fasting blood glucose, followed by HbA1c and waist circumference, suggesting that SFRP-4 may be particularly related to abnormalities in glucose regulation and central adiposity. These findings closely resemble the study by Sánchez-Pozos et al., in which SFRP-4 correlated positively with BMI, waist circumference, HbA1c, triglycerides and HOMA-IR [8].

The observed pattern is also biologically plausible because SFRP-4 has been implicated in Wnt signalling and metabolic inflammation. Recent evidence indicates that SFRP-4 may be increased in conditions characterized by obesity, inflammation and insulin resistance, while experimental studies suggest that it can

influence hepatic insulin action and lipid metabolism [3,12]. Furthermore, Sánchez-Pozos et al. found significant associations between SFRP-4 and inflammatory mediators including IL-6, IL-1 $\beta$  and IL-8, suggesting a possible connection between SFRP-4 and low-grade inflammation accompanying metabolic dysfunction [8]. Taken together, the present results indicate that elevated SFRP-4 is associated with several interconnected components of metabolic syndrome rather than with a single metabolic abnormality.

Overall, the findings of this study are consistent with growing evidence that circulating SFRP-4 is associated with obesity, impaired glucose regulation, insulin resistance and adverse lipid characteristics. However, because the present study is cross-sectional, the observed associations cannot establish whether increased SFRP-4 contributes directly to metabolic syndrome or instead reflects an underlying metabolic disturbance. Larger prospective studies incorporating insulin-resistance indices and inflammatory markers would therefore be useful to determine whether SFRP-4 has independent predictive value and whether it could eventually serve as a clinically useful biomarker.

## Conclusion

The present study demonstrated that serum SFRP-4 levels were significantly associated with several important metabolic abnormalities among subjects with metabolic syndrome. Higher SFRP-4 concentrations were observed in individuals with increased BMI, central obesity, elevated fasting blood glucose, higher triglycerides, low HDL-C, and hypertension. Significant positive correlations were also identified between SFRP-4 and BMI, waist circumference, fasting blood glucose, HbA1c, triglycerides, age, and systolic blood pressure, whereas HDL-C showed a significant inverse correlation. These findings suggest that elevated SFRP-4 may reflect the complex metabolic disturbances associated with obesity, insulin resistance, dysglycaemia, and adverse lipid profiles. Although the cross-sectional nature of

the study prevents establishing a causal relationship, the results support the potential role of SFRP-4 as a biomarker of metabolic dysfunction. Further prospective and larger-scale studies are warranted to clarify its clinical significance and potential usefulness in early identification and risk assessment of metabolic syndrome.

## Declarations

### Ethics Approval and Consent to Participate

The study was conducted at the Department of Biochemistry, Amar Shaheed Jodha Singh Ataiya Thakur Dariyao Singh Medical College, Fatehpur, Uttar Pradesh, India. Ethical approval was obtained from the Institutional Ethics Committee of the institution. Written informed consent was obtained from all participants before their inclusion in the study.

**Availability of Data and Materials:** The data supporting the findings of this study are available from the corresponding author upon reasonable request, subject to institutional policies and applicable ethical requirements.

**Competing Interests:** The authors declare that they have no competing interests related to this study.

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