# Secreted Frizzled-Related Protein 4 (SFRP4): A Novel Biomarker of β-Cell Dysfunction and Insulin Resistance in Individuals With Prediabetes and Type 2 Diabetes

*Kaviya Anand,[1] Sudha Vidyasagar,[2] Ian Lasrado,[2] Gautam Kumar Pandey,[1] Anandakumar Amutha,[1] Harish Ranjani,[1] Ranjit Mohan Anjana,[1] Viswanathan Mohan,[1] and Kuppan Gokulakrishnan[1]*

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Studying biomarkers early could help to identify high-risk individuals who could be targeted for the prevention of type 2 diabetes (T2D). Secreted frizzled-related protein 4 (SFRP4) is highly expressed in the islets, and its levels are increased several years before diabetes diagnosis (1). We report here on the systemic levels of SFRP4 and its association with insulin resistance and β-cell dysfunction.

Individuals with normal glucose tolerance (NGT; $n$ = 100), impaired glucose tolerance (IGT; $n$ = 60), and T2D ($n$ = 100) were recruited from a large tertiary diabetes center in Chennai and a medical college hospital at Manipal in southern India. NGT, IGT, and T2D were defined using World Health Organization consulting group criteria (2). β-Cell function and insulin resistance were calculated by the oral disposition index (DIo) and the HOMA of insulin resistance (HOMA-IR), respectively. SFRP4 levels were measured by ELISA.

A total of 260 individuals were included in the study, of whom 50% ($n$ = 130) were male. There were no significant differences in age, BMI, and sex between the three groups studied. However, waist circumference, fasting and 2-h postprandial plasma glucose, glycated hemoglobin, and HOMA-IR were significantly higher, and DIo lower, in individuals with IGT ($P < 0.01$) and T2D ($P < 0.001$). Among patients with T2D, 56 were on metformin, 25 were on sulfonylureas, and 19 were on both (Table 1).

Circulatory SFRP4 levels were highest in T2D (57 ± 7 ng/mL) followed by IGT (40 ± 4 ng/mL) and NGT (27 ± 2 ng/mL; $P < 0.001$). SFRP4 levels were positively

**Table 1—Clinical characteristics of study subjects**

| Variables | NGT ($n$ = 100) | IGT ($n$ = 60) | T2D ($n$ = 100) |
|---|---|---|---|
| Age (years) | 36 ± 12 | 34 ± 13 | 36 ± 13 |
| Male $n$ (%) | 49 (49) | 31 (51) | 50 (50) |
| BMI (kg/m$^2$) | 24.3 ± 2.9 | 25.0 ± 3.6 | 25.8 ± 3.8 |
| Waist circumference (cm) | 83.4 ± 11.1 | 89.5 ± 12.7** | 92.2 ± 9.7** |
| Systolic blood pressure (mmHg) | 120 ± 15 | 128 ± 18 | 121 ± 13 |
| Diastolic blood pressure (mmHg) | 76 ± 8 | 78 ± 10 | 79 ± 11 |
| SFRP4 levels (ng/mL) | 27 ± 2 | 40 ± 4* | 57 ± 7**# |
| HOMA-IR | 1.8 ± 0.64 | 4.1 ± 2.6** | 5.7 ± 3.3**# |
| DIo | 3.8 ± 1.9 | 1.5 ± 0.9* | 0.51 ± 0.32*# |
| Fasting blood glucose (mg/dL) | 86 ± 9 | 112 ± 14* | 154 ± 56**# |
| 2-h postprandial plasma glucose (mg/dL) | 103 ± 18 | 156 ± 24** | 249 ± 48**# |
| Glycated hemoglobin (%) | 5.5 ± 0.4 | 6.2 ± 0.6* | 7.6 ± 1.4**# |
| Glycated hemoglobin (mmol/mol) | 37 | 44 | 60**# |
| Fasting C-peptide (pmol/mL) | 0.9 ± 0.3 | 1.2 ± 0.5 | 1.3 ± 0.5**# |
| Stimulated C-peptide (pmol/mL) | 2.7 ± 0.9 | 3.2 ± 1.2 | 3.0 ± 1.0**# |
| Duration of T2D (years) | | | 2.1 ± 0.6 |
| Serum cholesterol (mg/dL) | 174 ± 34 | 190 ± 47 | 219 ± 49 |
| Serum triglycerides (mg/dL)^ | 122 ± 63 | 139 ± 74 | 173 ± 78 |
| LDL cholesterol (mg/dL) | 111 ± 28 | 123 ± 30 | 146 ± 33# |
| HDL cholesterol (mg/dL) | 39.6 ± 8.4 | 39.7 ± 10.6 | 37.6 ± 10.5 |
| Metformin, $n$ (%) | | | 56 (56) |
| Sulfonylurea, $n$ (%) | | | 25 (25) |
| Metformin + sulfonylurea, $n$ (%) | | | 19 (19) |

Data presented as mean ± SD, unless otherwise stated. ^Geometric mean. *$P < 0.01$; **$P < 0.001$ compared with NGT; #$P < 0.01$ compared with IGT.

[1]*Madras Diabetes Research Foundation and Dr. Mohan's Diabetes Specialities Centre, WHO Collaborating Centre for Noncommunicable Diseases Prevention and Control and International Diabetes Federation Centre of Education, Chennai, India*
[2]*Kasturba Medical College, Manipal, India*

*Corresponding author: Kuppan Gokulakrishnan, gokulmdrf@gmail.com or gokul@mdrf.in.*

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correlated with age ($P < 0.001$), HOMA-IR ($P < 0.001$), fasting plasma glucose ($P < 0.01$), fasting insulin ($P < 0.001$), glycated hemoglobin ($P < 0.001$), and serum triglycerides ($P < 0.01$) and inversely correlated with DIo ($P < 0.001$). There was no statistically significant difference in SFRP4 levels between the T2D patients on different antidiabetes agents, but this has to be further investigated in future studies.

In standardized polytomous regression models, higher levels of SFRP4 were independently associated with IGT (odds ratio [OR] per SD 1.39 [95% CI 1.15, 2.21]; $P < 0.01$) and T2D (OR 2.62 per SD [95% CI 1.48, 4.01]; $P < 0.01$) after controlling for age, sex, waist circumference, glycated hemoglobin, and DIo.

Early detection of ongoing β-cell dysfunction could allow for interventions before the development of overt diabetes (3). Cross-sectional studies indicate that Asian Indians may be susceptible to early decline in β-cell function even during stages of mild dysglycemia (4,5). In this context, this study assumes significance as we report increased SFRP4 levels in Asian Indians even at the stage of IGT. Increased SFRP4 levels were also positively correlated with fasting glucose, 2-h postprandial glucose, glycated hemoglobin, and HOMA-IR and inversely correlated with DIo.

These findings suggest that elevated SFRP4 may be a good marker of β-cell dysfunction and insulin resistance. However, our analyses are based on single measurements of SFRP4 and a cross-sectional study, which is a limitation. Longitudinal studies with serial measurements of SFRP4 need to be done at different stages of insulin resistance, IGT, and T2D to understand the precise pathophysiological mechanisms involved.

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**Author Contributions.** S.V., V.M., and K.G. conceived, initiated, supervised, conducted, and commented on all drafts of this paper. K.A., I.L., G.K.P., A.A., and K.G. coordinated the study and monitored all the data entry and work parts of the paper. K.A., S.V., H.R., R.M.A., and K.G. contributed extensively to the interpretative analysis of the data. S.V., V.M., and K.G. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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