Original Article

DOI: 10.7860/JCDR/2026/80073.22274

Biochemistry Section

Nesfatin-1 in Regulation of Glucose Homeostasis Across Different Stages of Glycaemia: An Observational Cross-sectional Study

R VASANTHAKUMARI[1], VM VINODHINI[2], P RENUKA[3], KA ARUL SENGHOR[4], JS KUMAR[5]

ABSTRACT

Introduction: Nesfatin-1 plays a crucial role in maintaining energy balance and regulating food intake through its action on both central and peripheral pathways. In addition to peripheral organs, including adipocytes, pancreatic islets, and stomach endocrine cells, it is primarily released by the hypothalamus. By encouraging peripheral glucose uptake and inhibiting gluconeogenesis, nesfatin-1 increases insulin sensitivity. Diabetes mellitus is preceded by prediabetes.

Aim: To compare nesfatin-1 in the regulation of glucose homeostasis across different stages of glycaemia.

Materials and Methods: This is an observational cross-sectional study conducted at the Department of Biochemistry, SRM Medical College Hospital and Research Centre, Kattankulathur, Chennai, Tamil Nadu, India, from May 2024 to March 2025. The study involved 90 adults, both men and women, aged 20 to 45 years. They were divided into three groups based on American Diabetes Association's (ADA) criteria into euglycaemic (HbA1c <5.7%), prediabetic (HbA1c 5.7-6.4%), and newly diagnosed type 2 diabetes (HbA1c ≥6.5%). Age, sex, height, weight, Body Mass Index (BMI), and Blood Pressure (BP) values were taken into account. Serum samples of the above individuals were separated and stored for analysing nesfatin-1 levels. Nesfatin-1 levels were analysed using the Enzyme-linked Immunosorbent Assay (ELISA) method. Statistical analysis was performed using IBM Statistical Package for Social Sciences (SPSS) software version 20.0. The three groups' continuous variables were compared using the Kruskal-Wallis test. The relationship between serum nesfatin-1 levels and metabolic markers was evaluated using Spearman's correlation. Statistical significance was established at a p-value of less than 0.05.

Results: Nesfatin-1 levels varied considerably among the three glycaemic groups (p-value=0.003), with newly diagnosed diabetics having median levels of 161.1 pg/mL, prediabetic people having 132.41 pg/mL and euglycaemic people having 149.28 pg/mL. Nesfatin-1 levels were lower in prediabetic individuals when compared to euglycaemic and newly diagnosed diabetic individuals. The prevalence of insulin resistance [Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) ≥2.9] was higher in newly diagnosed diabetics, 17/30 (57%), than in prediabetics, 4/30 (13%) and euglycaemics, 4/30 (13%). All groups had substantial prevalences of obesity (BMI ≥25 kg/m^2), 17/30 (57%) of euglycaemic people, 17/30 (57%) of prediabetic people, and 19/30 (63%) of newly diagnosed diabetic people. This suggests that insulin resistance and obesity play a part in early glucose dysregulation.

Conclusion: Early disruptions in glucose metabolism may be linked to altered nesfatin-1 levels. Increased BMI and HOMA-IR are important markers of type 2 diabetes progression, highlighting the necessity of early identification and individualised treatment plans.

Keywords: Adiposity, Biomarkers, Dysglycaemia, Insulin resistance

INTRODUCTION

Nesfatin-1 is a recently discovered 82-amino acid peptide, derived by post-translational modification of Nucleobindin-2 (NUCB2), a precursor protein found in the hypothalamus [1,2]. Nesfatin-1 acts as a satiety neuropeptide that induces feelings of fullness [3]. It is well-known for its ability to suppress appetite [4]. The sites of secretion are the hypothalamus, adipocytes, pancreatic islets and gastric endocrine cells. It is expressed about 20 times higher than in pancreatic islets when compared to other tissues [5]. Nesfatin-1 has been shown to enhance insulin sensitivity and glucose uptake through various signalling mechanisms, including its interactions with the hypothalamus and peripheral tissues [6].

The worldwide issue of diabetes continues to grow, with Type 2 Diabetes Mellitus (T2DM) accounting for over 90% of all cases. The International Diabetes Federation estimated that 537 million adults had diabetes in 2021 [7]. Projections show that this number could reach 783 million by 2045. This concerning trend highlights the need to find new biomarkers for early detection and intervention at the level of prediabetic state [8].

Nesfatin-1 improves insulin sensitivity by enhancing glucose uptake in the body and lowering gluconeogenesis. It influences glucose metabolism by phosphorylating specific signalling proteins through the activation of Adenosine Monophosphate-activated Protein Kinase (AMPK) [9]. The peptide has broad effects on metabolic balance. It helps modulate insulin secretion from pancreatic β-cells and boosts insulin release in response to glucose. Additionally, nesfatin-1 slows down movement in the stomach and duodenum, which contributes to its ability to promote fullness [10,11]. Apart from its role in managing glucose, nesfatin-1 plays important regulatory roles in adipogenesis and lipid metabolism, thus preventing metabolic syndrome and obesity [12].

Recent findings reveal that nesfatin-1 can affect heart regulation by activating different signalling pathways that help reduce oxidative stress in the heart muscle [13]. Moreover, new research suggests that nesfatin-1 might impact inflammatory pathways, possibly contributing to the low-grade inflammation seen in metabolic syndrome [14].

The mechanisms behind T2DM involve a complex mix of genetic, environmental, and metabolic factors [15]. Insulin resistance, which

often develops years before diabetes is diagnosed, is a crucial early event in this condition [16]. Recent diagnostic methods mainly focus on blood sugar levels, such as fasting plasma glucose, oral glucose tolerance tests, and glycated haemoglobin (HbA1c) [17]. However, these measures often reflect advanced metabolic issues rather than early signs of problems [18].

Prediabetes, a transitional state preceding overt diabetes, is characterised by impaired glucose metabolism and is strongly associated with metabolic syndrome and obesity [19]. Identifying biomarkers that signal early metabolic issues in prediabetics is essential for timely intervention [20]. Nesfatin-1 is one of the novel peptide hormones that have shown promise in identifying early abnormalities in glucose metabolism [21,22].

There are conflicting reports on nesfatin-1 levels in various glycaemic states. Some studies show higher levels in diabetic individuals [23], while others show lower levels [24]. This inconsistency may result from differences in study groups, research methods, or the state of metabolic dysfunction when the assessment was made.

The impact of peptide hormones like nesfatin-1 on the transition from prediabetes to diabetes is still not well understood in the Indian population, despite there are many studies on the effect of conventional biomarkers on other metabolic disorders worldwide [25,26].

This study analyses nesfatin-1 levels through the glycaemic spectrum in an Indian population. It provides valuable insights into how these biomarker patterns can vary by population. The study categorises participants based on HbA1c, insulin resistance (HOMA-IR), and BMI, offering a more comprehensive view of how nesfatin-1 relates to metabolic dysfunction. Thus, this study aims to assess changes in serum nesfatin-1 levels across different glycaemic states. The primary objective of the study is to compare serum nesfatin-1 levels among euglycaemic, prediabetic, and newly diagnosed type 2 diabetes mellitus patients, and to find their association with fasting plasma glucose, postprandial plasma glucose, HbA1c, HOMA-IR, and lipid profile. The secondary objective of the study was to compare serum Nesfatin 1 levels among the participants stratified on the basis of BMI and HOMA-IR (Homeostasis Model Assessment - Insulin Resistance) among various glycaemic groups.

MATERIALS AND METHODS

This observational cross-sectional study was conducted at the Department of Biochemistry, SRM Medical College Hospital and Research Centre (SRMMCH&RC), Chennai, Tamil Nadu, India, over a period of 11 months, from May 2024 to March 2025. The study was approved by the Institutional Ethics Committee (IEC No: SRMIEC-ST0224-928), and written informed consent was obtained from all participants before enrolment.

Sample size calculation: The sample size of 90 participants (30 per group) was calculated based on the study by Kadim BM and Hassan EA [27]. Using the effect size from that study, and considering a confidence interval of 95% and statistical power of 80%

Inclusion criteria: Individuals aged 20–45 years, classified into glycaemic groups according to their fasting plasma glucose and HbA1c levels, according to the American Diabetes Association (ADA) 2023 guidelines, were included.

Exclusion criteria: It comprised individuals with renal failure, hepatic failure, chronic inflammatory conditions, cardiovascular diseases, malignancies, haemoglobinopathies, anaemia, pregnancy, and those under treatment with statins, antiseizure drugs, antihypertensive agents, insulin sensitisers, steroids, or antimalarial medications.

Study Procedure

HbA1c-based stratification: According to the American Diabetes Association's (ADA) 2023 standards, participants were divided into three groups according to their glycaemic status:

- People who have an HbA1c of less than 5.7% and a Fasting Plasma Glucose (FPG) of less than 100 mg/dL are considered euglycaemic.
- People with FPG levels between 100 mg/dL and 125 mg/dL and/or HbA1c levels between 5.7% and 6.4% are considered prediabetic.
- People with FPG ≥126 mg/dL and/or HbA1c ≥6.5% who have never had diabetes before and are not taking any antidiabetic drugs at the time of enrollment are considered newly diagnosed type 2 diabetics (T2DM) [28].

HOMA-IR-based stratification: Further, this study group was stratified according to HOMA-IR levels. The Homeostasis Model Assessment (HOMA) is an index used to evaluate the interaction between glucose and insulin dynamics. HOMA-IR is a mathematical model that evaluates systemic insulin resistance. It is calculated using the formula:

$$\text{HOMA-IR} = \frac{[\text{Fasting Insulin } (\mu\text{IU/mL}) \times \text{Fasting Glucose (mmol/L)}]}{22.5,}$$

which provides an estimate of insulin resistance based on the interaction between fasting plasma glucose and fasting insulin concentrations.

BMI-based stratification: Based on BMI, again, this study group was stratified by BMI and was calculated as weight in kilograms divided by the square of the height in meters (kg/m^2). It is a predictor of obesity and metabolic syndrome.

As per Asian-Pacific guidelines, BMI < 18.5 kg/m^2 is underweight, BMI of 18.5–22.9 kg/m^2 is normal weight, BMI of 23-24.9 kg/m^2 is overweight and BMI ≥ 25 kg/m^2 [29].

Sample processing: The collected samples were allowed to clot for 30 minutes at room temperature, and then centrifuged at 3000 rpm for 10 minutes to separate serum. Serum was immediately aliquoted into pre-labelled Eppendorf tubes under sterile conditions.

Serum for nesfatin-1 analysis was aliquoted in 1 mL volumes and stored at –80°C to preserve peptide stability until analysis. Aliquots for insulin and lipid profile estimation were processed the same day.

Assay for nesfatin-1: Nesfatin-1 was measured using a competitive ELISA kit from ELK Biotechnology Co., Ltd. [30]. The procedure included the following steps, as per the manufacturer's instructions. To selected wells, 50 µL of the serum sample or standard was introduced. Each well received 50 µL of HRP-conjugate reagent. For 60 minutes, the plate was incubated at 37°C. Using an automated plate washer, wells were cleaned five times using the supplied wash buffer. After adding 50 µL of TMB substrates A and B, the mixture was incubated at 37°C for 15 minutes in the dark. A Bio-Rad ELISA reader was used to detect absorbance at 450 nm as soon as the reaction was stopped with 50 µL of stop solution. A standard curve produced by 4-parameter logistic regression was used to compute concentrations.

All assays were run in duplicates, and the mean value was taken for statistical analysis. Quality control samples with known concentrations were included to ensure intra-assay and inter-assay precision, which were within acceptable limits (<10%).

Insulin and Lipid Profile Estimation: Fasting insulin was measured by Chemiluminescent Immunoassay (CLIA) using the Beckman Coulter DXI 600 immunoassay system. Lipid profile parameters (total cholesterol, triglycerides, HDL-C, LDL-C) were analysed using the Beckman Coulter DXC 700 AU chemistry analyser, employing enzymatic colourimetric methods.

All instruments were calibrated prior to sample analysis using manufacturer-supplied calibration materials. Internal quality controls were used with each batch to ensure accuracy and reliability of results.

STATISTICAL ANALYSIS

Data distribution was evaluated using the Shapiro-Wilk test. Due to the non parametric nature of the data, the Kruskal-Wallis test was applied to compare variables across the three groups. Spearman's correlation was used to determine the strength and direction of associations between variables. All analyses were carried out using IBM SPSS Statistics, version 20.0 (IBM Corp., Armonk, NY, USA), and a p-value < 0.05 was considered statistically significant.

RESULTS

The study group comprised 30 euglycaemic, 30 prediabetic, and 30 newly diagnosed type 2 diabetic individuals. The comparison of the three groups stratified according to HbA1c, with values expressed as Median (interquartile range) are shown in [Table/Fig-1].

Nesfatin-1 levels were lower in prediabetic individuals when compared to euglycaemic and newly diagnosed diabetic individuals. The three groups differed significantly in Systolic Blood Pressure (SBP), nesfatin-1, FPG, Postprandial Plasma Glucose (PPPG), HbA1c, and HOMA-IR levels. Spearman's correlation was applied to understand the association of serum nesfatin-1 with HOMA-IR, FPG, PPPG, and HbA1c levels [Table/Fig-2]. No correlation was seen,

The study group was stratified based on HOMA-IR levels, resulting in 42 individuals within the normal HOMA-IR range (0.5-1.4), 23 individuals with early insulin resistance (≥1.9), and 25 individuals with established insulin resistance (≥2.9), as per HOMA-IR criteria.

The comparison of the three groups stratified according to HOMA-IR levels, with values expressed as median and Interquartile Range (IQR) presented in [Table/Fig-3].

The three groups differed significantly in weight, BMI, SBP, FPG, PPPG, HbA1c, Fasting insulin and HOMA-IR levels. The glycaemic status of the individuals was stratified based on HOMA-IR [Table/Fig-4].

Parameters	Euglycaemic (n=30)	Prediabetic (n=30)	Newly diagnosed T2DM (n=30)	p- value
Weight (kg)	67.3 (78.02,61.12)	68.55 (81.1,60.92)	69.1 (83.77,61.72)	0.801**
BMI (kg/m^2)	25.53 (28.29,22.64)	25.97 (30.49,23.43)	25.98 (30.65,23.65)	0.586**
Systolic BP (mmHg)	120 (130,110)	130 (130,120)	130 (130,120)	0.007*
Diastolic BP (mmHg)	80 (82.5,77.5)	85 (90,80)	80 (90,80)	0.062**
Nesfatin-1 (pg/mL)	149.28 (182.85,136.74)	132.41 (152.42,125.94)	161.1 (227.93,137.29)	0.003*
FPG (mg/dL)	91.5 (94.25,87)	96.5 (107,89)	152.5 (231.75,122.50)	<0.001*
PPPG (mg/dL)	105 (118.25,92.5)	120.5 (138.25,111.75)	254 (320.25,186.25)	<0.001*
HbA1c (%)	5.2 (5.4,4.9)	5.9 (6.1,5.8)	8.5 (10.65,7.05)	<0.001*
Fasting insulin (µIU/mL)	5.79 (9.05,3.25)	7.91 (11.38,5.94)	8.39 (10.85,4.75)	0.101**
HOMA-IR	1.30 (2.08,0.74)	1.92 (2.70,1.37)	3.05 (4.90,2.05)	<0.001*
Total cholesterol (mg/dL)	187 (211.25,166.5)	190.5 (197.5,152.75)	189.5 (215.75,157.75)	0.883**
Triglyceride (mg/dL)	108 (145.5,77.75)	104.5 (132.5,86)	114 (149.50,82.50)	0.909**
LDL-C (mg/dL)	134 (159,117.25)	128 (143,110.75)	133.5 (156.25,109.25)	0.506**
HDL-C (mg/dL)	48 (52.5,40)	43.5 (54.75,40)	45 (51.25,337.50)	0.727**
Hb (g/dL)	12.1 (14.2,11)	12.1 (14.15,11.2)	12.6 (14,11.5)	0.592**

[Table/Fig-1]: Comparison of anthropometric and biochemical parameters among euglycaemic, prediabetic and newly diagnosed type 2 diabetes mellitus patients using the Kruskal-Wallis Test.
Kruskal-Wallis Test; *p-value < 0.05 indicates statistical significance.
**- Non significant; Values are expressed as Median (Interquartile values); "BMI- Body mass index, BP-Blood pressure, FPG- Fasting plasma glucose, PPPG- Post prandial plasma glucose, HOMA-IR- Homeostatic Model Assessment of Insulin Resistance, LDL-C – Low density lipoprotein cholesterol, HDL-C - High density lipoprotein cholesterol, Hb- Haemoglobin"

	Euglycaemic (n=30)		Prediabetic (n=30)		Newly diagnosed (n=30)	
Parameters	Rho value	p-value	Rho-value	p-value	Rho-value	p-value
Weight (kg)	0.082	0.665**	0.124	0.512**	0.094	0.622**
BMI (kg/m^2)	0.035	0.853**	0.226	0.23**	-0.059	0.755**
Systolic BP (mmHg)	-0.078	0.683**	0.029	0.879**	0.104	0.585**
Diastolic BP (mmHg)	0.059	0.756**	0.197	0.296**	0.225	0.231**
FPG (mg/dL)	-0.169	0.373**	-0.289	0.122**	-0.018	0.924**
PPPG (mg/dL)	0.068	0.72**	-0.068	0.72**	0.024	0.901**
HbA1c (%)	0.041	0.831**	-0.212	0.26**	-0.141	0.457**
Fasting insulin (µIU/mL)	0.087	0.647**	-0.126	0.507**	-0.202	0.284**
HOMA-IR	0.061	0.751**	-0.153	0.419**	-0.236	0.21**
Total cholesterol (mg/dL)	0.294	0.114**	-.455*	0.011**	-0.229	0.224**
Triglyceride (mg/dL)	0.158	0.404**	-0.172	0.364**	0.051	0.787**
LDL-C (mg/dL)	0.287	0.123**	-.432*	0.017**	-0.274	0.143**
HDL-C (mg/dL)	-0.085	0.656**	-0.236	0.21**	0.163	0.389**
Hb (g/dL)	0.306	0.1**	0.116	0.541**	-0.113	0.551**

[Table/Fig-2]: Association of serum nesfatin-1 levels with HOMA-IR, FPG, PPPG and HbA1c levels in euglycaemic, prediabetic and newly diagnosed type 2 diabetes mellitus patients using Spearman's correlation.
Spearman's correlation; *p-value <0.05 indicates statistical significance. **-Non-significant; 'BMI- Body mass index, BP-Blood pressure, FPG- Fasting plasma glucose, PPPG- Post-prandial plasma glucose, HOMA-IR- Homeostatic Model Assessment of Insulin Resistance, LDL-C – Low density lipoprotein cholesterol, HDL-C - High density lipoprotein cholesterol, Hb- Haemoglobin'

Parameters	Normal (n=42)	Early Insulin resistance (n=23)	Insulin resistance (n=25)	p- value
Weight (kg)	65 (74.20,59.10)	73.1 (84.3,65.1)	71.3 (83.1,61.5)	0.033*
BMI (kg/m^2)	25.15 (27.96,22,21)	27.59 (31.93,23.91)	26.23 (31.21,24.41)	0.058*
Systolic BP (mmHg)	120 (130,110)	130 (130,130)	130 (130,120)	0.001*
Diastolic BP (mmHg)	80 (90,80)	80 (90,80)	80 (90,80)	0.231**
Nesfatin-1 (pg/mL)	148.96 (179.46,134.85)	145.34 (185.69,131.78)	152.27 (239.44,126.26)	0.971**
FPG (mg/dL)	92.5 (100,86)	99 (127,94)	134 (218.50,99.50)	<0.001*
PPPG (mg/dL)	114 (145.25,99.5)	127 (156,115)	209 (327.5,123)	<0.001*
HbA1c (%)	5.65 (6.10,5)	5.9 (6.7,5.7)	7.1 (10.2,5.85)	<0.001*
Fasting insulin (µIU/mL)	5.29 (6.38,3.14)	9.06 (9.85,8.11)	12.69 (16.34,9.26)	<0.001*
HOMA-IR	1.22 (1.58,0.77)	2.28 (2.72,2.08)	4.31 (5.33,3.53)	<0.001*
Total cholesterol (mg/dL)	188.5 (198.75,161.75)	170 (220,157)	193 (222,170.50)	0.221**
Triglyceride (mg/dL)	101 (134.25,85)	116 (137,84)	119 (166.5,84.5)	0.495**
LDL-C (mg/dL)	125.5 (148.75,114.50)	129 (160,95)	145 (161.5,119.5)	0.189**
HDL-C (mg/dL)	47.5 (11.5)	44 (51,40)	44 (58,39)	0.584**
Hb (g/dL)	12.2 (2.72)	13.4 (14.5,11.4)	12 (13.8,11.15)	0.471**

[Table/Fig-3]: Comparison of anthropometric and biochemical parameters among euglycaemic, prediabetic and newly diagnosed type 2 diabetes mellitus patients in individuals stratified on the basis of insulin resistance estimated by HOMA-IR using Kruskal-Wallis Test.
Kruskal-Wallis Test; *p-value<0.05 indicates statistical significance; **Non-significant; Values are expressed as Median (Interquartile values); BMI: Body mass index, BP: Blood pressure, FPG: Fasting plasma glucose, PPPG: Post-prandial plasma glucose, HOMA-IR: Homeostatic model assessment of insulin resistance, LDL-C: Low density lipoprotein cholesterol, HDL-C: High density lipoprotein cholesterol, Hb: Haemoglobin

Glycaemic status	No insulin resistance n (%)	Early insulin resistance n (%)	Insulin resistance n (%)
Euglycaemic (30)	21 (70%)	5 (17%)	4 (13%)
Prediabetic (30)	15 (50%)	11 (37%)	4 (13%)
Newly diagnosed T2DM (30)	6 (20%)	7 (23%)	17 (57%)

[Table/Fig-4]: Glycaemic status of the individuals stratified based on HOMA-IR.

Insulin resistance was more prevalent among newly diagnosed diabetic individuals, inferred from [Table/Fig-4]. Early insulin resistance is more prevalent among prediabetic individuals, and most of the euglycaemic individuals have no insulin resistance. The study group was stratified based on BMI as 22 individuals with normal BMI (18.5-22.9 kg/m^2), 15 overweight (23-24.9 kg/m^2) and 53 obese (≥25) stratified based on BMI. The comparison of three groups stratified based on BMI expressed in Median (Interquartile values) is shown in [Table/Fig-5].

The three groups varied significantly in weight, BMI, Fasting insulin, HOMA-IR, Total cholesterol, triglycerides and HDL-C levels.The glycaemic status of the individuals stratified based on BMI is shown in [Table/Fig-6].

Based on [Table/Fig-6], the authors inferred that there is a higher prevalence of obesity in all three groups, with the highest being in the newly diagnosed diabetic individuals.

DISCUSSION

Nesfatin-1, a novel neuropeptide, is involved in appetite regulation, enhancing insulin sensitivity, and glucose homeostasis [31]. It has gained attention as a potential biomarker in metabolic disorders recently [32]. There are many supporting studies of nesfatin-1 regarding its glycaemic control and metabolism [33,34].

This study analysed serum nesfatin-1 levels among euglycaemic, prediabetic, and newly diagnosed diabetics in the Indian population.

Parameters	Normal (n=22)	Overweight (n=15)	Obese (n=53)	P-value
Weight (kg)	58.4 (62.07,54.8)	63.9 (69.1,59)	77.7 (85,67.65)	<0.001*
BMI (kg/m^2)	21.9 (22.63,19.97)	24.35 (24.56,23.91)	28.5 (31.63,26.75)	<0.001*
Systolic BP (mmHg)	125 (130,120)	130 (130,120)	130 (130,120)	0.691**
Diastolic BP (mmHg)	80 (90,80)	80 (90,80)	80 (90,80)	0.512**
Nesfatin-1 (pg/mL)	146.02 (192.23,126.97)	140.92 (180.96,130.52)	148.49 (182.69,134.46)	0.788**
FPG (mg/dL)	97 (147.75,88.50)	94 (152,88)	98 (128,91)	0.762**
PPPG (mg/dL)	143.5 (218.25,107)	113 (222,113)	126 (192,104)	0.876**
HbA1c (%)	6 (8.57,5.17)	5.8 (7.4,5.2)	5.9 (6.9,5,5)	0.820**
Fasting insulin (µIU/mL)	5.13 (7.56,2.61)	8.24 (9.85,5.34)	8.31(12,5.75)	<0.001*
HOMA-IR	1.26 (2.63,0.57)	2.28 (3.63,1.22)	2.08 (3.39,1.56)	0.023*
Total cholesterol (mg/dL)	159 (191,144.50)	192 (212,183)	191 (220.5,167.50)	0.002*
Triglyceride (mg/dL)	88 (121.25,73)	134 (172,84)	112 (145,88)	0.023*
LDL-C (mg/dL)	109.5 (138,92.75)	143 (152,129)	134 (158,117.5)	0.350**
HDL-C (mg/dL)	44 (51.25,39.50)	42 (52,38)	48 (54,41)	0.004*
Hb (g/dL)	12.3 (13.65,11.15)	12.7 (15,11.8)	12.3 (14.05,11.15)	0.467**

[Table/Fig-5]: Comparison of anthropometric and biochemical parameters among euglycaemic, prediabetic and newly diagnosed type 2 diabetes mellitus patients stratified on the basis of BMI Kruskal-Wallis Test.
Kruskal-Wallis Test; *p-value < 0.05 indicates statistical significance. **Non significant; Values are expressed as Median (Interquartile values); 'BMI: Body mass index, BP: Blood pressure, FPG: Fasting plasma glucose, PPPG: Post-prandial plasma glucose, HOMA-IR: Homeostatic model assessment of insulin resistance, LDL-C: Low density lipoprotein cholesterol, HDL-C: High density lipoprotein cholesterol, Hb: Haemoglobin'

Glycaemic status	Normal BMI	Overweight	Obese
Euglycaemic (30)	7 (23%)	6 (20%)	17 (57%)
Prediabetic (30)	8 (27%)	5 (17%)	17 (57%)
Newly diagnosed T2DM (30)	7 (23%)	4 (13%)	19 (63%)

[Table/Fig-6]: Glycaemic status of the individuals stratified based on BMI:

This study revealed significant differences in nesfatin-1 levels across the three groups, with the highest levels observed in newly diagnosed T2DM patients. These findings contrast with Mirakhor Samani S et al., who reported lower serum nesfatin-1 levels in newly diagnosed type 2 diabetic patients when compared to healthy controls [35]. Similarly, Matta RA et al., also reported lower nesfatin-1 levels in diabetic and prediabetic individuals compared to healthy controls [36].

In contrast, Zhai T et al., observed elevated nesfatin-1 levels in newly diagnosed T2DM patients, which were consistent with our findings [37]. These discrepancies may be attributed to variations in ethnicity, sample size, BMI distribution, or the metabolic state at the time of sample collection. Study population variability and lower sample size are other probable causes.

Lower levels of nesfatin-1 in euglycaemic and prediabetic individuals may be due to the presence of underlying metabolic disorders like obesity, insulin resistance and chronic low-grade inflammation leading to dysregulated secretion of nesfatin-1 [38]. But the exact pathophysiological mechanisms are still remain unexplored. Some studies suggest that lower nesfatin-1 levels in normoglycaemic or prediabetic individuals may indicate early impairment in compensatory mechanisms or be influenced by underlying insulin resistance, obesity or chronic inflammation [39-41].

In the current study, however, nesfatin-1 levels did not show a significant association with glycaemic or lipid parameters, suggesting that its role may vary with disease stage or might be influenced by other modulating factors. To further explore the effect of metabolic risk, the participants were stratified by insulin resistance using HOMA-IR. A significant proportion of prediabetic and T2DM participants exhibited elevated HOMA-IR, supporting its role as an early predictor of glycaemic dysfunction [42,43]. This is in line with long-term cohort studies by Lee J et al., and Khalili D et al., which demonstrated a strong association between elevated HOMA-IR and progression to T2DM [44,45]. So, HOMA-IR can also be utilised as a valuable tool for early detection of individuals at risk of developing diabetes.

Similarly, BMI-based stratification revealed a high prevalence of obesity, particularly among newly diagnosed diabetics. This supports the well-established role of obesity in promoting insulin resistance via impaired insulin receptor and Glucose Transporter Type 4 (GLUT-4) expression [46]. Longitudinal analyses, such as the study by Hassanloo N et al., have shown that increasing BMI trajectories significantly raise the risk of developing diabetes, even among normoglycaemic individuals [47].

Interestingly, several studies have found that people with lower BMIs, especially those from East Asian communities, had higher glycaemic variability, even though higher BMI is generally associated with insulin resistance [48]. This implies that, through potentially distinct mechanisms, both high and low BMI may negatively impact glucose regulation. The relationship between BMI and glycaemic status has important clinical implications, as both high BMI and low BMI with glycaemic variability require tailored strategies to prevent or manage T2DM [49].

Limitation(s)

The present study was limited by its single-centre design; therefore, larger multicentric studies are recommended to validate and strengthen these findings.

CONCLUSION(S)

In conclusion, the current findings suggest that nesfatin-1 is associated with dysglycaemia. This points to its potential role not just in understanding how diabetes develops, but also in identifying it earlier. With more research, nesfatin-1 could become a useful marker or even a target for future diabetes treatments. A higher HOMA-IR and BMI are risk factors for progression of prediabetes to diabetes. Routine HOMA-IR monitoring and weight management are vital for timely intervention and prevention of diabetes.

REFERENCES

[1] Alotibi MN, Alnoury AM, Alhozali AM. Serum nesfatin-1 and galanin concentrations in the adult with metabolic syndrome. Relationships to insulin resistance and obesity. Saudi Med J. 2019;40(1):19-25. Doi: 10.15537/smj.2019.1.22825. PMID: 30617376; PMCID: PMC6452611.

[2] Sun J, Zhang D, Xu J, Chen C, Deng D, Pan F, et al. Circulating FABP4, nesfatin-1, and osteocalcin concentrations in women with gestational diabetes mellitus: A meta-analysis. Lipids Health Dis. 2020;19(1):199. Doi: 10.1186/s12944-020-01365-w. PMID: 32861247; PMCID: PMC7456504.

[3] García-Galiano D, Navarro VM, Roa J, et al. The anorexigenic neuropeptide, nesfatin-1, is indispensable for normal puberty onset in the female rat. J Neurosci. 2010;30(23):7783-92. Doi: 10.1523/JNEUROSCI.5828-09.2010.

[4] Strnadová V, Pačesová A, Charvát V, et al. Anorexigenic neuropeptides as anti-obesity and neuroprotective agents: Exploring the neuroprotective effects of anorexigenic neuropeptides. Biosci Rep. 2024;44(4):BSR20231385. Doi: 10.1042/BSR20231385.

[5] Ayada C, Toru Ü, Korkut Y. Nesfatin-1 and its effects on different systems. Hippokratia. 2015;19(1):4-10.

[6] Salama A, Elhini S, Moaness H, Abdelhaleem W. Assessment of Plasma level of Nesfatin-1 in newly diagnosed Type 2 Diabetic patients. Minia J Med Res. 2019;30(1):78-81. Doi: 10.21608/mjmr.2022.22277.

[7] Ong KL, Lin JK, Lim YN, Afshin A, Bennitt FB, Bragg F, et al. Global, regional, and national burden of diabetes from 1990 to 2021, with projections of prevalence to 2050: A systematic analysis for the Global Burden of Disease Study 2021. Lancet. 2023;402(10397):203-34. Doi: 10.1016/S0140-6736(23)01301-6.

[8] Xu L, Sun X, Wang N, et al. Risk factor assessment of prediabetes and diabetes based on epidemic characteristics in new urban areas: A retrospective and a machine learning study. Sci Rep. 2025;15:3792. Doi: 10.1038/s41598-025-88073-6.

[9] Damian-Buda AC, Matei DM, Ciobanu L, et al. Nesfatin-1: A novel diagnostic and prognostic biomarker in digestive diseases. Biomedicines. 2024;12(8):1913. Doi: 10.3390/biomedicines12081913.

[10] Rupp SK, Wölk E, Stengel A. Nesfatin-1 receptor: Distribution, signaling and increasing evidence for a G protein-coupled receptor—a systematic review. Front Endocrinol (Lausanne). 2021;12:740174. Doi: 10.3389/fendo.2021.740174. PMID: 34566899; PMCID: PMC8461182.

[11] Xia ZF, Fritze DM, Li JY, et al. Nesfatin-1 inhibits gastric acid secretion via a central vagal mechanism in rats. Am J Physiol Gastrointest Liver Physiol. 2012;303(5):G570-7. Doi: 10.1152/ajpgi.00178.2012.

[12] Ramanjaneya M, Chen J, Brown JE, Tripathi G, Hallschmid M, Patel S, et al. Identification of nesfatin-1 in human and murine adipose tissue: A novel depot-specific adipokine with increased levels in obesity. Endocrinology. 2010;151(7):3169-80. Doi: 10.1210/en.2009-1358.

[13] Fan Z, Dong J, Mu Y, Liu X. Nesfatin-1 protects against diabetic cardiomyopathy in the streptozotocin-induced diabetic mouse model via the p38-MAPK pathway. Bioengineered. 2022;13(6):14670-81. Doi: 10.1080/21655979.2022.2066748.

[14] Mohammed ZH, Allwsh TA. Nesfatin-1: Relation to oxidative stress and inflammation markers for newly diagnosed myocardial infarction patients in Mosul/Iraq. J Med Pharm Chem Res. 2025;7(4):570-80. Doi: 10.48309/jmpcr.2025.455961.1219.

[15] Galicia-Garcia U, Benito-Vicente A, Jebari S, et al. Pathophysiology of type 2 diabetes mellitus. Int J Mol Sci. 2020;21(17):6275. Doi: 10.3390/ijms21176275.

[16] DeFronzo RA. The triumvirate: β-cell, muscle, liver. A collusion responsible for NIDDM. Diabetes. 1988;37(6):667-87. Doi: 10.2337/diab.37.6.667.

[17] American Diabetes Association. 2. Classification and diagnosis of diabetes: Standards of Medical Care in Diabetes—2024. Diabetes Care. 2024;47(Suppl 1):S21-30. Doi: 10.2337/dc24-S002.

[18] Garber AJ, Handelsman Y, Grunberger G, et al. Consensus statement by the AACE and ACE on the comprehensive type 2 diabetes management algorithm - 2020 Executive Summary. Endocr Pract. 2020;26(1):107-39. Doi: 10.4158/CS-2019-0472.

[19] Echouffo-Tcheugui JB, Selvin E. Prediabetes and what it means: The epidemiological evidence. Annu Rev Public Health. 2021;42:59-77. Doi: 10.1146/annurev-publhealth-090419-102644. PMID: 33355476; PMCID: PMC8026645.

[20] Khan RMM, Chua ZJY, Tan JC, et al. From pre-diabetes to diabetes: Diagnosis, treatments and translational research. Medicina (Kaunas). 2019;55(9):546. Doi: 10.3390/medicina55090546.

[21] Tabák AG, Herder C, Rathmann W, et al. Prediabetes: A high-risk state for diabetes development. Lancet. 2012;379(9833):2279-90. Doi: 10.1016/S0140-6736(12)60283-9.

[22] Grundy SM. Pre-diabetes, metabolic syndrome, and cardiovascular risk. J Am Coll Cardiol. 2012;59(7):635-43. Doi: 10.1016/j.jacc.2011.08.080.

[23] Zhang Z, Li L, Yang M, Liu H, Boden G, Yang G. Increased plasma levels of nesfatin-1 in patients with newly diagnosed type 2 diabetes mellitus. Exp Clin Endocrinol Diabetes. 2012;120(2):91-5. Doi: 10.1055/s-0031-1286339. PMID: 22020667.
[24] Li QC, Wang HY, Chen X, Guan HZ, Jiang ZY. Fasting plasma levels of nesfatin-1 in patients with type 1 and type 2 diabetes mellitus and the nutrient-related fluctuation of nesfatin-1 level in normal humans. Regul Pept. 2010;159(1-3):72-7. Doi: 10.1016/j.regpep.2009.11.003.
[25] Huang K, Liang Y, Ma Y, et al. The variation and correlation of serum adiponectin, nesfatin-1, IL-6, and TNF-αlevels in prediabetes. Front Endocrinol (Lausanne). 2022;13:774272. Doi: 10.3389/fendo.2022.774272. PMID: 35311231; PMCID: PMC8928772.
[26] Kadoglou NPE, Korakas E, Lampropoulos S, et al. Plasma nesfatin-1 and DPP-4 levels in patients with coronary artery disease: Kozani study. Cardiovasc Diabetol. 2021;20(1):166. Doi: 10.1186/s12933-021-01355-x. PMID: 34389003; PMCID: PMC8362239.
[27] Kadim BM, Hassan EA. Nesfatin-1—as a diagnosis regulatory peptide in type 2 diabetes mellitus. J Diabetes Metab Disord. 2022;21(2):1369-75. Doi: 10.1007/s40200-022-01070-8.
[28] American Diabetes Association Professional Practice Committee. 2. Classification and diagnosis of diabetes: Standards of Medical Care in Diabetes-2022. Diabetes Care. 2022;45(Suppl 1):S17-38. Doi: 10.2337/dc22-S002. PMID: 34964875.
[29] MoncadaLim JU, Lee JH, Kim JS, et al. Comparison of World Health Organization and Asia-Pacific body mass index classifications in COPD patients. Int J Chron Obstruct Pulmon Dis. 2017;12:2465-75. Doi: 10.2147/COPD.S141295.
[30] ELK Biotechnology Co., Ltd. Human Nesfatin-1 (NES1) ELISA Kit [Internet]. Wuhan, China: ELK Biotechnology Co., Ltd.; [cited 2025 Jul 25]. Available from: https://www.elkbiotech.com/pro/ELK8190
[31] Stengel A. Nesfatin-1 - more than a food intake regulatory peptide. Peptides. 2015;72:175-83. Doi: 10.1016/j.peptides.2015.08.010.
[32] Schalla MA, Stengel A. Current understanding of the role of nesfatin-1. J Endocr Soc. 2018;2(10):1188-206. Doi: 10.1210/js.2018-00246.
[33] Khalili S, Khaniani M, Afkhami F, Derakhshan S. NUCB2/Nesfatin-1: A potent meal regulatory hormone and its role in diabetes. Egypt J Med Hum Genet. 2017;18(1):105-10. Doi: 10.1016/j.ejmhg.2016.10.003.
[34] Khalil UA, Mohamed OE, Abdullah AA, et al. Do serum nesfatin-1 levels have a predictive role in type 2 diabetes mellitus and its microvascular complications? A case-control study. Cureus. 2024;16(1):e53007. Doi: 10.7759/cureus.53007. PMID: 38406171; PMCID: PMC10894677.
[35] Mirakhor Samani S, Ghasemi H, Rezaei Bookani K, Shokouhi B. Serum nesfatin-1 level in healthy subjects with weight-related abnormalities and newly diagnosed patients with type 2 diabetes mellitus: A case-control study. Acta Endocrinol (Buchar). 2019;15(1):69-73. Doi: 10.4183/aeb.2019.69. PMID: 31149062; PMCID: PMC6535324.
[36] Matta RA, El-Hini SHE, Salama AMS, et al. Serum nesfatin-1 is a biomarker of pre-diabetes and interplays with cardiovascular risk factors. Egypt J Intern Med. 2022;34:15. Doi: 10.1186/s43162-022-00102-2.
[37] Zhai T, Li SZ, Fan XT, Tian Z, Lu XQ, Dong J. Circulating nesfatin-1 levels and type 2 diabetes: A systematic review and meta-analysis. J Diabetes Res. 2017;2017:7687098. Doi: 10.1155/2017/7687098.
[38] Tekin T, Cicek B, Konyaligil N. Regulatory peptide nesfatin-1 and its relationship with metabolic syndrome. Eurasian J Med. 2019;51(3):280-4. Doi: 10.5152/eurasianjmed.2019.18420.
[39] Yang M, Zhang Z, Wang C, et al. Nesfatin-1 action in the brain increases insulin sensitivity through Akt/AMPK/TORC2 pathway in diet-induced insulin resistance. Diabetes. 2012;61(8):1959-68. Doi: 10.2337/db11-1755.
[40] Anwar GM, Yamamah G, Ibrahim A, El-Lebedy D, Farid TM, Mahmoud R. Nesfatin-1 in childhood and adolescent obesity and its association with food intake, body composition and insulin resistance. Regulatory Peptides. 2014 Jan 10;188:21-24. Doi: 10.1016/j.regpep.2013.12.001
[41] Algul S, Ozkan Y, Ozcelik O. Serum nesfatin-1 levels in patients with different glucose tolerance levels. Physiol Res. 2016;65(6):979-85. Doi: 10.33549/physiolres.933186. PMID: 27539099.
[42] Wallace TM, Levy J, Matthews DR. Use and abuse of HOMA modelling. Diabetes Care. 2004;27(6):1487-95. Doi: 10.2337/diacare.27.6.1487.
[43] Quesada O, Claggett B, Rodriguez F, et al. Associations of insulin resistance with systolic and diastolic blood pressure: A study from the HCHS/SOL. Hypertension. 2021;78(3):716-25. Doi: 10.1161/HYPERTENSIONAHA.120.16905.
[44] Lee J, Kim MH, Jang JY. Assessment of HOMA as a predictor for new onset diabetes mellitus and diabetic complications in non-diabetic adults: A KoGES prospective cohort study. Clin Diabetes Endocrinol. 2023;9:7. Doi: 10.1186/s40842-023-00156-3.
[45] Khalili D, Khayamzadeh M, Kohansal K. Are HOMA-IR and HOMA-B good predictors for diabetes and pre-diabetes subtypes? BMC Endocr Disord. 2023;23:39. Doi: 10.1186/s12902-023-01345-9.
[46] Cignarelli A, Genchi VA, Perrini S, et al. Insulin and insulin receptors in adipose tissue development. Int J Mol Sci. 2019;20(3):759. Doi: 10.3390/ijms20030759.
[47] Hassanloo N, Mehran L, Amouzegar A, et al. Association between body mass index trajectories and type 2 diabetes incidence over an 18-year follow-up in the Tehran Lipid and Glucose Study. Sci Rep. 2024;14(1):27615. Doi: 10.1038/s41598-024-75179-6.
[48] Shamanna P, Dharmalingam M, Sahay R. Retrospective study of glycemic variability, BMI, and blood pressure in diabetes patients in the Digital Twin Precision Treatment Program. Sci Rep. 2021;11:14892. Doi: 10.1038/s41598-021-94391-4.
[49] Lipsky LM, Gee B, Liu A, Nansel TR. Glycemic control and variability in association with body mass index and body composition over 18 months in youth with type 1 diabetes. Diabetes Res Clin Pract. 2016;120:97-103. Doi: 10.1016/j.diabres.2016.07.028.

PARTICULARS OF CONTRIBUTORS:
1. Postgraduate Student, Department of Biochemistry, SRM Medical College Hospital and Research Centre, Chennai, Tamil Nadu, India.
2. Professor and Head, Department of Biochemistry, SRM Medical College Hospital and Research Centre, Chennai, Tamil Nadu, India.
3. Professor, Department of Biochemistry, SRM Medical College Hospital and Research Centre, Chennai, Tamil Nadu, India.
4. Professor, Department of Biochemistry, SRM Medical College Hospital and Research Centre, Chennai, Tamil Nadu, India.
5. Professor and Head, Department of General Medicine, SRM Medical College Hospital and Research Centre, Chennai, Tamil Nadu, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. VM Vinodhini,
Professor and Head, Department of Biochemistry, SRM Medical College Hospital and Research Centre, Chennai-603203, Tamil Nadu, India.
E-mail: vinodhiv1@srmist.edu.in

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: May 12, 2025
- Manual Googling: Nov 03, 2025
- iThenticate Software: Nov 05, 2025 (13%)

ETYMOLOGY: Author Origin

EMENDATIONS: 7

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Apr 21, 2025**
Date of Peer Review: **Jul 22, 2025**
Date of Acceptance: **Nov 07, 2025**
Date of Publishing: **Jan 01, 2026**