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ORIGINAL ARTICLE

# Role of stanniocalcin-1 and proenkephalin-A as novel biomarkers in prediction of newly diagnosed type 2 diabetic patients

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## Abstract

**Background** Diabetes mellitus is a chronic metabolic disorder that carries substantial implications for health, social well-being, and economic factors. Stanniocalcin-1 STC-1 is a polypeptide hormone that was initially distinguished as a controller of calcium/phosphate homeostasis in the fish. There is a growing evidence that human STC-1, an autocrine/paracrine factor, plays a role in both inflammation and carcinogenesis. The stable fragment proenkephalin-A (PENKA) is a novel biomarker derived from the precursor enkephalin, which is involved in multiple biological pathways.

**Objective** The objective of this study was to assess the significance of two newly discovered biomarkers, stanniocalcin-1 and proenkephalin-A, in patients recently diagnosed with type 2 diabetes.

**Methods** The study consisted of 90 participants, who were divided into two groups. The first group comprised 60 patients with recently diagnosed T2DM, while the second group consisted of 30 healthy individuals serving as controls. The age range of the participants spanned from 35 to 65 years.

**Result** The study found a significant increase in body mass index (BMI), fasting blood glucose (FBG), HbA1c, C-peptide, HOMA-IR, total cholesterol (TC), triglyceride (TG), LDL, VLDL, stanniocalcin-1, and proenkephalin-A in patients with newly DM when compared with those in the control group. Also, there was a significant increase in HDL levels in the control group compared to the newly diagnosed diabetic group.

**Conclusions** In conclusion, the results of our study indicate that stanniocalcin-1 and proenkephalin-A could potentially be used as indicators of glucose homeostasis. Consequently, these biomarkers may offer an alternative to conventional markers in predicting risk factors for diabetes mellitus.

**Keywords** Diabetes mellitus · Stanniocalcin-1 · Proenkephalin-A · Lipid profile · HOMA-IR

## Introduction

Diabetes mellitus (DM) is a chronic endocrine disease that is characterized by high blood sugar levels. This condition occurs due to either insufficient production of insulin by the pancreas or reduced sensitivity of the body to insulin, or both [1]. Insufficient activity of insulin on target tissue, due to insulin insensitivity or absence, leads to disturbances in carbohydrate, protein, and fat metabolism. Type 2 diabetes affects individuals of various age groups and has significant implications for morbidity, mortality, and healthcare expenses for patients, their families, and countries. A study conducted in 2013 revealed that it impacted 382 million people (7.7% of the population), with projections estimating a continuous increase to 483 million (8.3%) by the year 2030. In developed nations, a majority of individuals diagnosed with T2DM are over the age of 65, while only 8% are under

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the age of 44 [2]. Insulin resistance characterization of type 2 diabetic is associated with a progressive decay of β-cell function in pancreas. T2DM is additionally connected to an expanded danger of cardiovascular comorbidities and cardiovascular disease [3]. Stanniocalcin-1 STC-1 is an autocrine/paracrine factor in mammalian that regulates calcium/phosphate homeostasis and was first segregated in fish. The STC hormone family, which consists of STC-1 and STC-2, is commonly expressed in mammalian tissues. However, limited knowledge exists regarding the impact of STC on lipid metabolism [4, 5]. Mammalian STC-1 is communicated in different tissues, including hormone responsive organs and the endocrine glands. Among all tissues, the ovaries contain the most levels of stanniocalcin-1 expression, with raised expression observed during lactation and pregnancy [4]. Furthermore, STC expression has been confirmed in the tissue of pancreas; in fact, STC-1 has described to be expressed together with insulin in the β cells of the pancreas islets [6]. STC is found in various bodily tissues of animals and acts as a paracrine/autocrine factor. Recent research has indicated that the expression of STC-1 is associated with several pathological processes and diseases, including tumor development, inflammation, and metastasis [5]. Proenkephalin-A PENKA is a peptide (approximately 4.5 kDa) [7, 8]. The human proenkephalin is composed of 267 amino acids. It is found in various locations within the nervous system, including the adrenal medulla, bone-derived cells, and different cells of the immune system [9, 10]. Pancreatic islets cells additionally generate proenkephalins, which block the absorption of glucose and hence decrease the insulin response. Moreover, several additional physiological impacts have been documented, such as its impact on blood pressure and heart rate [11]. Plasma can be used to quantify PENKA, a reliable and stable substitute for the enkephalins. The precursor molecule proenkephalin is synthesized in various cells throughout the human body, including both neuronal and non-neuronal cells [12]. The precursor molecule, proenkephalin, is synthesized in various cells within the human body, both neuronal and non-neuronal. The study is aim to assess the significance of two newly discovered biomarkers, stanniocalcin-1 and proenkephalin-A, in patients recently diagnosed with type 2 diabetes.

## Material and methods

### Study design

A case control study was conducted with a total of 90 participants, based on ADA criteria for diagnosis of DM 2022 [13]. The first group consisted of 60 individuals who had recently been diagnosed with T2DM (newly DM), while the second group included 30 healthy subjects. The age range of the participants was between 35 and 65 years, and the healthy subjects were matched in age to the control group for comparison. The exclusion criteria included the following: patients with diabetic group have no other disease like hypertension, ischemic heart disease, and thyroid dysfunction. The study, which took place at the national diabetes center of Mustansiriyah University from July to September 2023.

### Ethical approval

The research was conducted in line with the Helsinki Declaration. Obtained informed consent from all participants prior to their involvement. Furthermore, the study received ethical approval from the ethics committee of the national diabetes center.

### Collection of a blood samples

The samples were collected from individuals who had fasted for 8–12 h between the hours of 8:30 and 11:30 a.m. The blood was divided into two parts. One part, consisting of 1 mL, was transferred into an EDTA tube for the measurement of HbA1C. The other part, consisting of 9 mL, was transferred to a gel tube. Two milliliters of serum from this part were used for the measurement of FBG and lipid profile. The remaining portion was transferred to a tube and stored at − 20 °C for further investigation, specifically C-peptide, stanniocalcin-1, and proenkephalin-A.

### Anthropometries measurement

We measured age, weight, and height of the participants. The BMI was calculated by dividing the weight (in kilograms) by the square of the height (in meters).

### Measurement of the homeostasis model assessment (HOMA-IR)

Various methods were employed to evaluate insulin resistance (IR) in the research, with the prevailing method being the utilization of homeostasis model assessment (HOMA). HOMA involves the computation of fasting insulin (U/ml) and glucose (mg/dl), as depicted in the subsequent equation [14].

$$\mathbf{HOMA/IR} = \mathbf{[g(mg/dl) \times fasting\ insulin\ (\mu U/ml)]/405}$$

### Clinical laboratory analysis of groups

The FBG, lipid profile tests (Biolabo, France) were assessed using an enzymatic technique. The HLC-723GX was based

on the high-performance liquid chromatography HPLC was used to determine HbA1c. Enzyme-linked immune sorbent assay (ELISA) was used to assess C-peptide (Human, USA), stanniocalcin-1, and proenkephalin-A (Al-shkairate-Jordon).

### Statistical analysis

The statistical analysis was conducted using SPSS 22.0.0 (2018), Chicago, IL, USA. The significance level was set at $p < 0.05$. Unpaired *t*-tests were employed to examine differences among multiple groups, assuming a normal distribution and the absence of significant outliers. To assess the ability of various parameters to distinguish active cases from control, receiver operator characteristic curves (ROC) were utilized.

## Result

### Anthropometrics and biochemical parameters of study groups

The level of (BMI, FBG, HbA1c, C-peptide, and HOMA-IR) showed a highly significant increase ($p < 0.001$) in newly diagnosed DM as compared to control group as illustrated in Table 1.

The result of the study as shown in the Table 2, demonstrated a highly increase significant ($p < 0.001$) in newly diagnosed DM (TC, TG, LDL, and VLDL) as compared to control group. Also, the current study revealed a statistically significant increase ($p < 0.001$) in the mean levels of HDL in the control group. Conversely, the mean levels of HDL were lower in the newly diagnosed DM group.

### Serum stanniocalcin-1 and proenkephalin-A of study groups

Serum (stanniocalcin-1 and proenkephalin-A) was significantly higher $p < 0.001$ in newly diagnosed DM (1200.2 ± 353.2 and 737.8 ± 254.4) compared to control group (701.6 ± 223.1 and 484.3 ± 283.2).

**Table 1** Anthropometrics and biochemical parameters of study groups

| Variables | Newly DM ($N=60$) | Control ($N=30$) 30 | *p*-value |
|---|---|---|---|
| Age years | 52.4 ± 8.9 | 50.1 ± 9.4 | NS |
| BMI kg/m$^2$ | 32.1 ± 7.1 | 25.8 ± 4.1 | < 0.001 |
| FBG (mg/dl) | 200.2 ± 50.15 | 88.6 ± 7.8 | < 0.001 |
| HbA1c % | 8.6 ± 1.2 | 4.8 ± 0.6 | < 0.001 |
| C-peptide (ng/ml) | 2.3 ± 0.7 | 1.7 ± 0.6 | < 0.001 |
| HOMA-IR | 3.8 ± 1.8 | 2.2 ± 0.5 | < 0.001 |

All data represent as mean ± SD. *BMI* body mass index, *FBS* fasting blood glucose

**Table 2** Assessment of lipid panel biochemical parameters of study groups

| Variables | Newly DM ($N=60$) | Control ($N=30$) | *p*-value |
|---|---|---|---|
| TC (mg/dl) | 176.9 ± 30.3 | 140.8 ± 20.5 | < 0.001 |
| TG (mg/dl) | 155.0 ± 30.8 | 88.6 ± 25.9 | < 0.001 |
| HDL (mg/dl) | 39.7 ± 8.5 | 47.1 ± 5.8 | < 0.001 |
| LDL (mg/dl) | 109.2 ± 33.5 | 84.1 ± 24.3 | < 0.001 |
| VLDL (mg/dl) | 28.7 ± 12.6 | 16.2 ± 3.9 | < 0.001 |

All data represent as mean ± SD. *TC* total cholesterol, *TG* triglyceride

### Receiver operating characteristic curve analysis (ROC)

Stanniocalcin-1 demonstrated significant capability when comparing newly diagnosed DM with the control group, exhibiting high sensitivity and specificity (≥ 90%), as well as high accuracy (≥ 80%). Proenkephalin-A also exhibited a favorable ability to distinguish between newly diagnosed DM and the control group, with high sensitivity and specificity (≥ 80%) and accuracy (≥ 80%), as indicated in Table 3 and Figs. 1 and 2.

## Discussion

Glycated hemoglobin serves as an indicator of blood glucose levels within the preceding 3-month period. In cases where hemolytic anemia medications or kidney dysfunction are present, HbA1c measurements may potentially underestimate the true extent of blood glucose levels [15, 16]. HbA1c testing is significant as it tests chronic glycemia in patients with diabetes. It has been used as an objective criterion for normal glycemic regulation in diabetes patient management [17]. Insulin and connection peptide (C-peptide) are secreted by the pancreatic β cells [18, 19]. C-peptide, especially after glucagon stimulation or a mixed meal, is considered a reliable tool for estimating the residual function of β cells [18, 20]. According to numerous studies, C-peptide is a biologically active peptide. It has been proven to mitigate the inflammation resulting from hyperglycemia and provide protection against diabetic complications in individuals with diabetes mellitus (DM) [20–22]. The findings of this study are consistent with our previous research [22–24], which observed elevated levels of TC,TG, and LDL, as well as reduced levels of HDL cholesterol, among T2DM. By reducing glucose absorption in peripheral tissues and boosting glucose synthesis in the liver, insulin resistance causes high blood glucose levels. Insulin resistance induces heightened

**Table 3** AUC and validity of stanniocalcin-1 and proenkephalin-A to differentiate between patients and control groups

| Variables | Cut-off value | AUC | SN | SP | AC | PPV | NPV |
|---|---|---|---|---|---|---|---|
| Stanniocalcin-1 | < 897.5 | 0.974 | 96.8 | 90.5 | 93.7 | 90.8 | 97.4 |
| Proenkephalin-A | < 767. < | 0.850 | 83.1 | 83.2 | 83.2 | 83.2 | 83.2 |

*AUC* area under the curve, *SN* sensitivity, *SP* specificity, *AC* accuracy, *PPV* positive predictive value, *NPV* negative predictive value

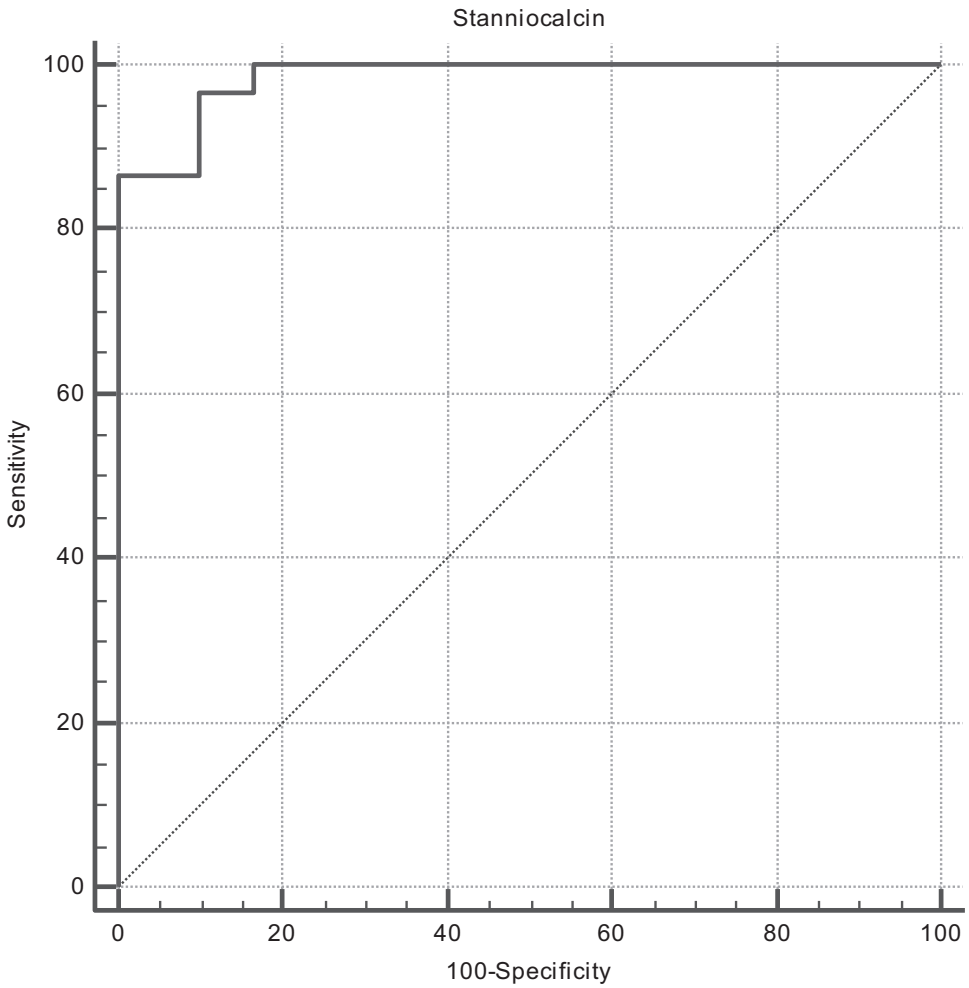


**Fig. 1** The ROC curve for stanniocalcin-1 newly diagnosed DM with control group

adipocyte lipolysis and the subsequent release of free fatty acids, along with increased hepatic lipid production. Mammalian stanniocalcin-1 STC-1 is a glycoprotein hormone with antioxidant and anti-inflammatory properties that is involved in calcium control. STC-1 has recently been shown to attenuate the development of ROS and the activation of inflammatory pathways by inducing mitochondrial [25–27]. The binding of STC-1 to the cell surface leads to the activation of mitochondria. Based on subcellular fractionation, it is indicated that more than 90% of cellular STC-1 exhibits immunoreactivity in the mitochondrial fraction [23, 28, 29]. The reduction of hypercalcemia tends to be the main feature of STC, close to that of calcitonin. STC and calcitonin both possess antihypercalcemic properties, although STC exhibits a greater efficacy compared to calcitonin. Furthermore, the expression of human STC-1 is not limited to a specific organ; rather, it is predominantly expressed in various tissues including the thyroid gland, ovary, and prostate [30]. Zaidi, D. et al. [31], showed that STC-1 and insulin have collocated strongly in adult mouse pancreatic β cells. Since the majority of the cellular insulin is restricted to secretory vesicles, much of the immunoreactivity of STC-1 with insulin appears to exist therein. The STC-1 transcript receptor is predominantly located in the β cells of the pancreas, suggesting its involvement in intracrine signaling. However, the specific functions of this receptor in β-cells remain

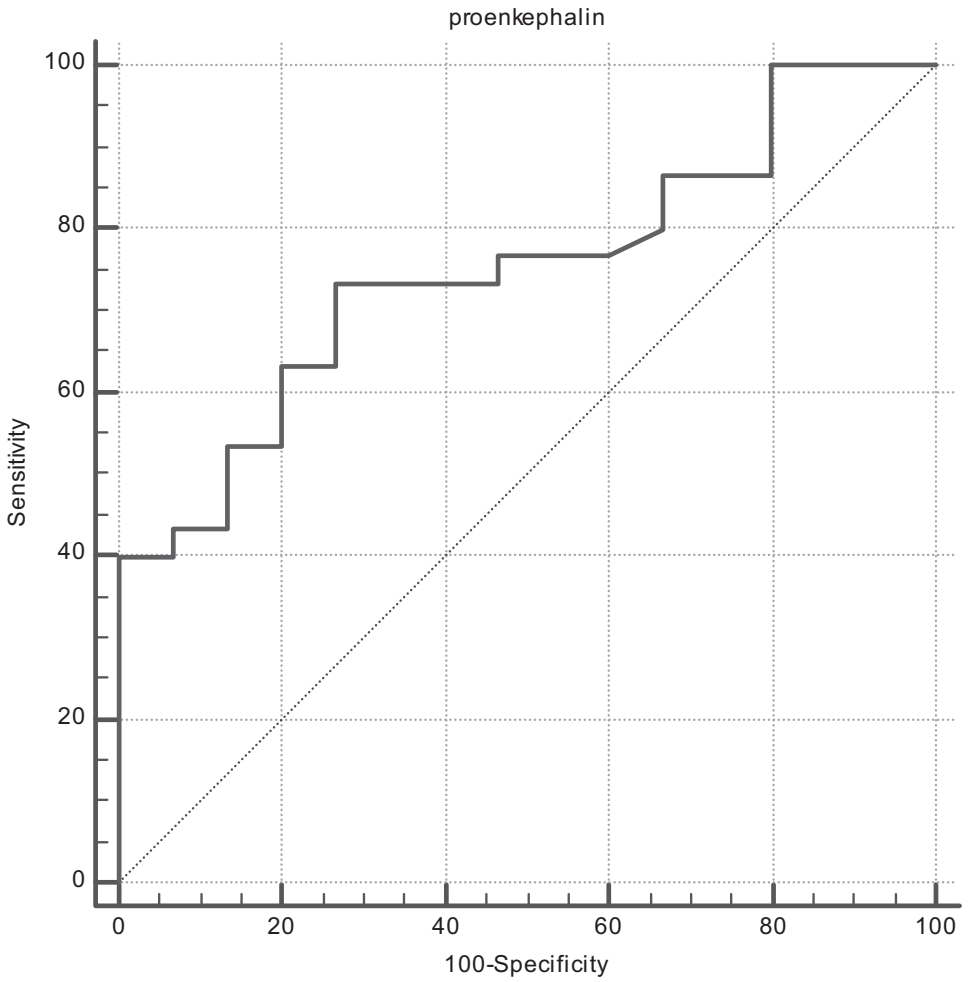


**Fig. 2** The ROC curve for proenkephalin-A in newly diagnosed DM with control groups

speculative [32]. Sarapio, E. et al. [33] showed that human STC-1 could be new signaling elements for the regulation of blood glucose levels in the postprandial period by rising glucose uptake in adipose tissue. In addition, Schein, V. et al. [34] found that STC-1 reduced renal gluconeogenic activity in rats, indicating that these hormones are involved in mammalian homeostasis of blood glucose. The decrease in gluconeogenesis in the kidneys and the rise in glucose absorption by STC-1 hormones in adipose tissue play a crucial role in maintaining glucose balance in mammals, particularly individuals with T2DM. The precursor molecule of the enkephalin family is proenkephalin-A [35, 36]. It is located mostly in the cell matrix and is also present in the nucleus, membrane, and mitochondria of the cell. It also serves as a neurotransmitter, encoding a preproprotein that was proteolytically processed to generate multiple kinds of protein products [37, 38]. The peptides derived from proenkephalin-A function as neuromodulators, neurotransmitters, and neurohormones. They demonstrate opioid activity and have effects on pain responses, stress responses, sleep, and appetite control [39]. The opioid peptide enkephalin is found in brain and endocrine tissues and has effects on nociceptive and neuroendocrine responses [40]. Enkephalin is produced by cells in the pancreatic islets and functions to inhibit insulin response by blocking glucose absorption. Furthermore, enkephalin has been found to have various physiological effects, including its influence on blood pressure and heart rate [41]. The effects of enkephalin and morphine were blocked by the specific opiate antagonist naloxone hydrochloride ($1.2 \times 10^{(-6)}$ mol/l). The insulin secretory response of perfused islets to enkephalins and morphine was rapid, corresponding to the first phase of glucose induced insulin release. These observations suggest that there may be opiate receptors in islets, and that opioid peptides could modulate insulin release [11]. The direct effects of an enkephalin analogue on insulin release from isolated islets of Langerhans of the rat have been investigated. It had a dose-dependent effect on insulin secretion [42]. Opioid peptides are localized within the hypothalamus and, thus, are likely involved in modulating homeostatic signals received from the peripheral tissues, pharmacological studies have shown that opioid receptor agonists stimulate food intake, while opioid receptor antagonists suppress food intake. However, the role of each opioid peptide in feeding behavior and, notably,

glucose homeostasis is not fully understood [43]. Marino, R. et al., Shah, KS.et al., Hollinger, A, et al., and Beunders, R, et al. [44–47] found that plasma proenkephalin is elevated in patients with acute or chronic renal failure compared to healthy controls. The proposed pathophysiological pathway for proenkephalin may have prognostic value in predicting mortality and worsening renal function. This pathway could be attributed to the cardio depressive effects of enkephalins, which may lead to decreased kidney perfusion and advanced heart failure. It is difficult to explain properly the real mechanism through which the biomarkers staninocalcin-1 and proenkephalin-A affect the immune process and glucose homeostasis in diabetic patients and some information may be missed because these markers are novel and there is a lack of references and researchers about them which make it difficult to understand their clear role in pathophysiology. There are certain limitations, it is a cross-sectional study with no follow-up conducted at a single center, and a bit small sample size.

## Conclusion

Our results reveal a potential role of proenkephalins and STC-1 in the regulation of glucose homeostasis and in the pathophysiology of diabetes type 2. Stanniocalcin-1 and proenkephalin-A are the most specific and sensitive markers in a newly diagnosed type 2 diabetic. Stanniocalcin-1 and proenkephalin-A are a sign of glucose homeostasis, and hence may serve as a substitute for all other conventional biomarkers in the prediction of risk factors for diabetes mellitus. Our suggestion of measurement of these biomarkers may have utility as novel biomarkers of the newly diagnosed type 2 diabetic.

**Author contributions** The authors contributed to this work.

### Declarations

**Ethics approval** The research was conducted in line with the Helsinki Declaration. Obtained informed consent from all participants prior to their involvement. Furthermore, the study received ethical approval from the ethics committee of the national diabetes center.

**Conflict of interests** The authors declare no competing interests.

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