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Humanin, the Mitochondrial derived peptide, and its role in type 2 diabetes

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Abstract–*Mitochondria, an important organ, play a critical role in production and metabolism of energy, oxidative stress, apoptosis, and homeostasis of calcium also, mitochondria dysfunction linked to age-related-diseases such as type 2 diabetes. Mitochondria produce bioactive small peptide called humanin encoded by mitochondrial DNA (mtDNA), mitochondria own circulating genome, have many physiological functions: its work as ani-oxidant by inhibition the generation of ROS, anti-apoptosis, anti-inflammatory agent, induces insulin sensitivity, improves B cell survival, delay diabetes development and promote glucose metabolism, in this study we determined humanin concentration in type 2 diabetic patients and compared with control healthy, and study the relationship between humanin and some clinical variables such as age, sex, smoking, BMI, blood types, nutrition, menopause, duration of disease, diabetes complication, family history, physical activity, medicine, HOMA-IR and HbA1C%. The results showed a significant decrease in humanin concentration in diabetes patients compared to control group, its concentration negatively correlated with sex, age, smoking, BMI, duration of disease, HOMA-IR, HbA1C%, diabetic retinopathy while humanin concentration positively correlated with menopause, increased physical activity, metformin, but there was a non-significant correlation with blood types, nutrition, family history. We suggested Humanin to be a biomarker of type 2 diabetes and its complication.*

Keywords: *Humanin, Oxidative stress, Risk factors, Type 2 diabetes.*

Abbreviations and notation: ROS, Reactive oxygen species; HOMA-IR, Homeostasis model assessment for insulin resistance; mtDNA, mitochondrial DNA; BMI, Body mass index; T2D, Type 2 diabetes; HOMA-β, homeostasis model assessment for beta-cell.

1) INTRODUCTION

Type 2 diabetes (T2D) and its complications are a world health problem, it happens when the pancreas produce insufficient amounts of insulin, and the body becomes resistant to insulin [1] its usually diagnosed in middle age, and characterized by high blood glucose and insulin resistance [2, 3]. Mitochondria play key role in regulation of bioenergy metabolism, producing of reactive oxygen species, regulation of apoptosis pathways and glucose metabolism, Mitochondria function strongly related to level of blood glucose and type 2 diabetes [4, 5]. Mitochondria produce microprotein called humanin which have biological activity [6] . humanin considered the first peptide derived from mitochondria. It has neuroprotective, anti-oxidant and anti-inflammations effects. It is produced by tissues in many organs, including the kidneys, skeletal muscles, liver, brain, and heart. it is secreted into the blood circulation and transported to many target cells [7 - 9]. It consists of 24 amino acids encoded in the 16s rRNA region of mtDNA. Humanin contains three regions: Positively charged amino terminal (Met-Ala-Pro -Arg), Negatively charged carbon terminal (Pro – Val – Lys -Arg -Arg- Ala), And a central hydrophobic region (Gly-Phe-Ser-Cys-Leu-Leu-Leu-Leu-Thr-Ser-Glu-Ile-Asp-Leu) [5, 10]. Humanin reduces oxidative stress, decrease apoptosis of beta cell, delay diabetes development, induce mitochondrial biosynthesis, enhances fatty acid metabolism, and affect concentrations of plasma amino acid, Humanin involved in several clinical diseases. Humanin levels may be indicator of type 2 diabetes [11 , 12]

2) Experimental

(a) Samples prepetition

Blood samples were collected from 35 healthy people (male and female) and 55 patients with type 2 diabetes (male and female) with ages from (20-76) years for each group. They were collected from Al-Wafa

Specialized Center for Diabetes and Endocrinology in Mosul city, the serum was isolated and kept under -20 C° and later the following variables were estimated

(b) Methods

humanin concentration was determined using the Bioanalytical Technology Laboratory kit (China) by the enzyme-linked immunosorbent assay technique (ELISA), glucose, Creatine, urea, total cholesterol (TC), triglycerides (TG) and HDL-C were determined using BIOLABO kit (France), Insulin was estimated using Monobind kite (American), HbA1C% was determined using Latex-Enhanced Immunoturbidimetric Assay by cobas HbA1C% kit (Germmany)) , VLDL, LDL, Homeostasis model assessment for insulin resistance (HOMA-IR), homeostasis model assessment for beta-cell function (HOMA-β), QUICKI were calculated using following equation:

$$\text{VLDL-C(mmol/L)} = \frac{\text{TG(mmol/L)}}{2.2}$$

Friedewald equation: LDL (mmol/L) = Conc. Of total Cholesterol – HDL –VLDL

HOMA-IR = fasting insulin (μU/ mL) ×fasting glucose (mmol/ L)/22.5

HOMA-β (%) = fasting insulin (μU/ mL)× 20/ (fasting glucose (mmol/ L)-3.5)

QUICKI = 1/ [log fasting insulin (uU/ml) + log fasting glucose(mg/dl)]. [13]

Body Mass Index calculated using the equation:

$$BMI = \frac{W(kg)}{L^2(m^2)}$$

Many risk factors have been studied such as age, sex, smoking, BMI, blood Types, nutrition, menopause in women, duration of disease, disease complication, family history, physical activity, treatment drugs, HMOA-IR and HbA1C%

Table 1. clinical Characteristics of patients and control

Clinical variables	**Control group mean± S. E**	**Patients mean± S. E**
Glucose	4.80 ± 0.89	10.96 ± 1.13 **
Insulin	10.02 ± 0.21	8.036 ± 0.51 *
HOMA-IR	2.13 ± 0.04	3.95 ± 0.45 **
Quickie	0.340 ± 0.001	0.319 ± 0.005 **
B-cell-function	177.6 ± 32.38	24.16 ± 3.45 ***
urea mmol/l	4.09 ± 0.24	5.70 ± 0.42 **
creatinine μmol/l	59.86 ± 3.26	69.05 ± 7.33
urea/creatinine ratio	71.70 ± 5.83	88.85 ± 5.61 *
cholesterol mmol/l	4.67 ± 0.24	5.10 ± 0.30
TG mmol/l	1.47 ± 0.15	2.54 ± 0.30 **
VLDL mmol/l	0.67 ± 0.07	1.15± 0.13 **
LDL mmol/l	2.49 ± 0.16	4.05 ± 0.63 *
HDL mmol/l	1.15 ± 0.05	0.89 ± 0.06 **
HbAc1 %	5.36 ± 0.05	8.64 ± 0.32 ***

* Significant variance p≤ 0.05, and ** P≤0.01, and *** p≤ 0.001

(c) Data analysis

We used SPSS program to analyze our data, the results represented as mean ± standard error. T-test used to compare two variations and ANOVA one way used to analyze more than two variants, P ≤ 0.05 regarded statistically significant. Receiver operating characteristic (ROC) curves were used and the area under the curve (AUC) to assign HbA1C% and HOMA-IR values in patients and healthy control also, we used Youden's index to determine the cutoff value

3) Results And Discussion

(a) Humanin concentration in patients with DM and control group

Humanin showed significantly decrease in patients compared to control group as in Table 2 and that agree with [3] because, in T2D, mitochondria number and ATP production decreased, so humanin concentration decreases or may be because high production of ROS and oxidative stress and reduction of mitochondrial DNA (mtDNA) content in skeletal muscle which correlate with Insulin resistance [3, 5].

Table 2. Humanin concentration in T2D patients and control group

Humanin Conc.(ng/ml) mean± S. E	
Control	Patients
69.71 ± 7.8	45.42 ± 2.5 **

** significant at P≥0.01, S. E=stander Error

(b) Humanin concentration and effects of some risk factors in T2D

As showed in Table 3 healthy females showed significantly less concentration of humanin comparing with males and that may be due to the inhibitory effect of estrogen since the ovarian steroid's hormones inhibit the humanin expression or may be due to stimulatory action of androgens [14].

The results had shown a significant decline in humanin concentration in patients with (> 61 years) compared with (20-40 years) and that because the dysfunction of mitochondria can be found in many diseases that related to age such as T2D which effects on humanin concentration [15]. The smoking patients showed decline in humanin level compared with non-smoking, cigarette smoking cause increase in oxidative stress, ROS, mitochondria damage and dysfunction which in turn, decline humanin level [16], humanin levels negatively correlated with oxidative stress [17].

Table 3. Humanin Concentration according to clinical variables

Variables	Humanin (ng/ml) mean±S.E	
	Control	Patients
Males	89.67 ± 13.4	48.10 ± 1.5
Females	54.48 ± 4.09 **	42.39 ± 5.0
Age (years) 20-40	78.26± 6.898	54.84± 2.812
41-61	84.26± 11.22	47.54± 0.8614
>61	50.36± 1.182 *	36.65± 5.524 **
non-smokers	72.08 ± 6.89	53.73 ± 4.79
Smokers	67.34 ± 5.86	37.42 ± 3.79 *
BMI 18.5-24.9 (healthy weight)	83.22± 13.25	49.2± 2.373
25-29.9 (overweight)	77± 4.264	52.35±3.601
≥ 30 (obesity)	50.12± 2.338 *	34.69± 5.523 *
Blood Type A	71.81± 9.075	51.63± 5.403
B	64.56 ± 7.186	41.83± 5.282
AB	73.1 ± 9.287	45.35± 2.872
O	70.31 ± 12.51	42.93± 6.092
Premenopausal women	49.42 ± 2.3	36.95 ± 2.9
Postmenopausal women	61.44 ± 4.8 *	47.83 ± 6.69
Physical activity Yes	80.65 ± 8.53	51.97 ± 2.68
No	58.77 ± 5.46 *	38.60 ± 3.96 **
Diet Yes	68.72 ± 11.13	42.39 ± 5.08
No	70.96 ± 11.4	48.10 ± 1.55

*Significant variance at p≤ 0.05, and ** at P≤0.01

Obesity effect on humanin levels in both patients and healthy control. In patients and control groups, the obese showed significantly decline in humanin concentration compared with healthy weight and that agree with humanin negatively correlated with BMI [18, 19] mitochondrial dysfunction promotes the metabolic disorders pathogenesis and affected tissues such as adipose, skeletal muscle and liver, results in accumulation of lipid and insulin resistance [20]. Humanin concentration showed non-significant differences between patients and controls according to blood type. In patients, humanin increased significantly in postmenopausal compared with premenopausal women, and that coordinate with Mitochondria play a pivotal role in steroid hormones synthesis including estrogen. in turn, these hormones are able to effect on mitochondrial functions humanin expression inhibited by estrogen so, the decline in circulating estrogen can promote the release of GnRH from hypothalamic which in turn can increases humanin expression [21]. Our results showed that physically active healthy and patients (walking for half an hour daily) have significant increase in humanin level compared to non- physically active persons, humanin is exercise- sensitive peptide, expression of muscles and plasma humanin is upregulated responding to exercise within 10 min, the exercise contraction suppress the degrading of humanin leading to increase humanin in circulation [22]. There was a non-significant difference between patients and controls according to diet. Patients who have duration of disease (> 15) years and (5-15) years showed significantly decrease cutting-edge humanin compared to patients who have (< 5) years as in Table 4. As the disease progress and the complications of the disease increased, hyperglycemia cause an increase in oxidative stress and mitochondrial dysfunction, Serum humanin is negatively correlated with oxidative stress and inflammation [15, 17, 23].

Table 4. Humanin Concentration in patients according to duration the disease

Variables	Humanin (ng/ml) mean±S.E
Duration of disease < 5 years	57.38 ± 3.985
5 -15 years	41.18± 3.918 *
>15 years	36.45± 3.635 **
Complication Retinopathy	36.76± 3.518
Nephropathy	50.9± 5.746 *
Neuropathy	49.57± 2.48 *
family history Yes	48.73 ± 4.56
No	42.44 ± 2.75
Medicines Metformin	54.50 ± 4.06
Sitagliptin	38.96 ± 2.64 **

Significant variance at p≤ 0.05, and ** at P≤0.01

Diabetic retinopathy patients showed a significant decrease in humanin level compared with neuropathy and nephropathy patients, Diabetic retinopathy defined as a common complication of diabetes and the cause of losing vision, clinically, Diabetic retinopathy is a microvascular disease cause retinal capillaries damage with impairment of secondary visual. Diabetes induces oxidative stress also, mitochondrial are important sources of ROS because of their key role in oxidative metabolism. Oxidative stress generated in mitochondria can contribute to the damages of retinal microvasculature [24], humanin levels negatively correlated with oxidative stress [17]. Family history showed a non- significant difference in humanin concentration. Patients who treated with metformin showed a significant high humanin

concentration than patients who treated with sitagliptin. Metformin and sitagliptin are anti-diabetes lowering glucose drugs, metformin was reported to decline blood glucose, decrease insulin resistance, improve insulin sensitivity more than sitagliptin [25, 26].

(c) The curve of received operating characteristic (ROC) of humanin level to diagnosis diabetes:

The ROC curve as in Figure. 3 used to find the optimum cutoff for stratifying diabetes patients from healthy control, the area under the curve (AUC) was 0.7238; 95% confidence interval, 0.0.6128 to 0.8347; ($p < 0.001$). Sensitivity (0.6863) and Specificity (0.764) and the cutoff value of humanin for discriminating between diabetes patient and control (50.04 ng/ml).

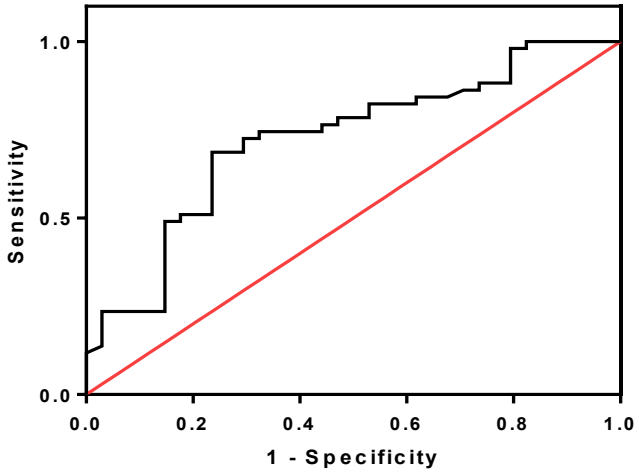

Figure. 1 the ROC curve of humanin

Also, Figure. 2 and 3 showed the ROC curve of HMOA-IR and HbA1C% respectively, the optimum cutoff for HMOA-(2.72) and for HbA1C% (6.2). Patients with HOMA-IR > 2.7 showed significantly decline in humanin concentration compared to patients with HOMA-IR < 2.7 as in Table 5 and that consistent with [10].

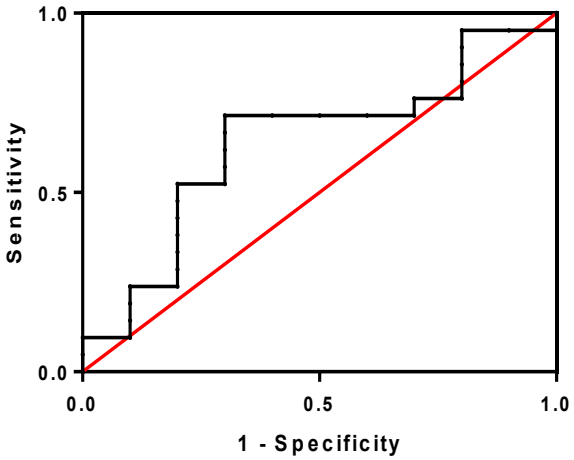

Figure. 2 ROC curve of HMOA-IR

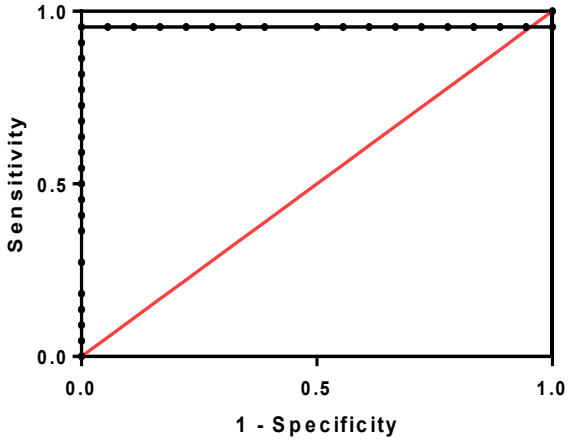

Figure. 3 the ROC curve of HbA1C%

Table 5. Humanin concentration in patients according to HbAc1%

HMOA-IR < 2.7	55.67 ± 3.36
> 2.7	37.79 ± 3.00 **

HbA1C% < 6.5	51.41 ± 3.26
> 6.2	38.67 ± 3.51 *

* Significant variance at p≤ 0.05, and ** at P≤0.01

humanin encoded by mtDNA which is mitochondria own genomes [27], mitochondria contain mtDNA copies about tens to thousands per cell, decreases mtDNA copies are associated with decreased humanin levels [28] insulin resistance causes mitochondria dysfunction and decrease mtDNA copies which in turn cause decline of humanin level [29, 30].

(4) CONCLUSIONS

Humanin concentration decreased in type 2 diabetes patients compared to healthy control, its concentration negatively correlated with sex, age, smoking, BMI, duration of disease, HOMA-IR, HbA1C%, diabetic retinopathy and positively correlated with menopause, increased physical activity, metformin, Humanin could be biomarker of type 2 diabetes and its complication.

(5) Acknowledgement

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(6) Conflict of Interests

The is no conflict of interest.

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