Indonesian Journal on Health Science and Medicine
Vol. 3 No. 1 (2026): July

ISSN 3063-8186 (online), https://ijhsm.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

Indonesian Journal on Health Science and Medicine

Vol. 3 No. 1 (2026): July

Table Of Contents

ISSN 3063-8186 (online), https://ijhsm.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

Originality Statement

The author[s] declare that this article is their own work and to the best of their knowledge it contains no materials previously published or written by another person, or substantial proportions of material which have been accepted for the published of any other published materials, except where due acknowledgement is made in the article. Any contribution made to the research by others, with whom author[s] have work, is explicitly acknowledged in the article.

Conflict of Interest Statement

The author[s] declare that this article was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright Statement

Indonesian Journal on Health Science and Medicine

Vol. 3 No. 1 (2026): July

EDITORIAL TEAM

Editor in Chief

Section Editor

Complete list of editorial team (link)

Complete list of indexing services for this journal (link)

How to submit to this journal (link)

Indonesian Journal on Health Science and Medicine

Vol. 3 No. 1 (2026): July

Article information

Check this article update (crossmark)

Check this article impact (*)

Save this article to Mendeley

(*) Time for indexing process is various, depends on indexing database platform

ISSN 3063-8186 (online), https://ijhsm.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

Indonesian Journal on Health Science and Medicine
Vol. 3 No. 1 (2026): July

Association of Age with Metabolic Biomarkers and Insulin Resistance in Patients with Type 2 Diabetes in Basrah, Iraq

Mohammed Adil Abdulhassan, Mohammed.adel@uobasrah.edu.iq (*)
1Al-Zahra ,a Medical College - University of Basrah, Basrah, Iraq

Shurok Namah khudair, edc0096@mtu.edu.iq
Iraqi Ministry of Health, Basrah Health Directorate, Basrah, Iraq

Khairallah A.S Mohammed, dr.kmohammed@stu.edu.iq
College of Health and Medical Techniques /Basra, Southern Technical University, Basra, Iraq

Abdulaziz Qadori Abdulsada, pgs.abdulaziz.qadori@uobasrah.edu.iq
Iraqi Ministry of Health, Basrah Health Directorate, Basrah, Iraq

(*) Corresponding author

Abstract

General Background: Type 2 diabetes mellitus (T2DM) is an age-related metabolic disorder characterizedbyprogressivemetabolicdeterioration.**SpecificBackground:** Orexin-Aandcathepsin-D have been implicated in hypothalamic regulation and cellular quality control, yet their age-related alterations in T2DM remain insufficiently characterized. **Knowledge Gap:** The interplay between aging, hypothalamic dysfunction, and cellular stress markers in relation to insulin resistance has not been comprehensively explored. **Aims:** This study investigated age-associated changes in orexin-A and cathepsin-D and their correlations with insulin resistance in T2DM patients. **Results:** A cross-sectional analysis of 110 T2DM patients and 70 controls revealed a significant age-related decline in orexin-A levels (69% reduction, p=0.001) and an increase in cathepsin-D levels (p=0.005). Orexin-A showed a negative correlation with insulin resistance (r = -0.26, p = 0.005), whereas age and cathepsin-D were positively correlated with HOMA-IR. Traditional metabolic markers, including HbA1c, triglycerides, and LDL, worsened with age. Regression analysis identified age, BMI, and cathepsin-D as positive predictors, while orexin-A was a negative predictor of insulin resistance. **Novelty:** This study identifies a previously unreported relationship between declining orexin-A and increasing cathepsin-D levels as age progresses in T2DM. **Implications:** These findings highlight the relevance of age-specific metabolic pathways and suggest the need for tailored therapeutic approaches in older diabetic populations.

Highlights:
- Progressive reduction of orexin-A observed across advancing age groups
- Increasing cathepsin-D levels linked to worsening metabolic profiles
- Age and biomarker patterns associated with higher insulin resistance

Keywords: Type 2 Diabetes Mellitus, Aging, Orexin-A, Cathepsin-D, Insulin Resistance

ISSN 3063-8186 (online), https://ijhsm.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

Indonesian Journal on Health Science and Medicine

Vol. 3 No. 1 (2026): July

Published date: 2026-04-06

ISSN 3063-8186 (online), https://ijhsm.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

Introduction

Type 2 diabetes mellitus (T2DM) is among the most prevalent age-related metabolic disorders, with its prevalence rising exponentially after the fifth decade of life [1], [2]. Although the association between aging and increased diabetes risk is well established, the molecular mechanisms underlying age-related metabolic decline remain incompletely defined [3]. Emerging evidence indicates that aging disrupts multiple interconnected pathways, including hypothalamic regulation and cellular quality-control mechanisms [4], [5].

The hypothalamic neuropeptide orexin-A plays a crucial role in energy homeostasis, glucose metabolism, and the maintenance of insulin sensitivity [6]. Orexin neurons within the lateral hypothalamus project extensively throughout the brain and control food intake, energy expenditure, and glucose balance via the autonomic nervous system [7]. Age-related reductions in orexin-producing neurons have been linked to metabolic dysfunction; however, their specific contribution to the progression of diabetes remains poorly characterized [8].

Cathepsin-D, a lysosomal aspartyl protease, has emerged as a key marker of cellular stress and impaired protein degradation in metabolic disorders [9]. Under physiological conditions, cathepsin-D supports cellular homeostasis by degrading misfolded proteins and damaged organelles through autophagy [10]. In the diabetic state, however, chronic hyperglycemia and oxidative stress promote lysosomal dysfunction and aberrant cathepsin-D activity, which can exacerbate cellular injury and insulin resistance [11], [12].

Despite these insights, the interplay among aging, hypothalamic dysfunction, and cellular stress responses in T2DM has not been comprehensively explored. Elucidating these age-related alterations is critical for developing targeted interventions for the growing population of elderly individuals with diabetes. The present study therefore investigated age-associated patterns of orexin-A and cathepsin-D, alongside conventional metabolic parameters, to determine their relationships with insulin resistance in a well-characterized cohort from Basrah, Iraq.

Materials and Methods

This cross-sectional study was carried out between February and September 2023 at the Faiha Specialized Diabetes, Endocrine and Metabolism Center (FDEMC), Basrah, Iraq (ethical approval: 2906). A total of 110 patients with T2DM and 70 healthy controls (32 to 70) participated in the study. Patients were separated into four age categories: <40 (n = 23), 40-49.9 (n = 36), 50-59.9 (n = 24) and 60 and above (n = 27).

Five milliliters of fasting blood were put ready to be examined. Orexin-A and cathepsin-D, HbA1c, insulin/C-peptide, and glucose/lipids were measured using ELISA (MyBioSource), HPLC (VARIANT 2 TURBO), and electrochemiluminescence (COBAS e411) and enzymatic, respectively. The HOMA-IR formula was (insulin 405/glucose). The statistical analysis with the use of SPSS v25 relied on Spearman correlation ($p<0.05$) and non-parametric tests.

Study Design and Participants

A cross-sectional study was conducted at the FDEMC, Basrah, Iraq, from February to September 2023 (ethical approval No. 2906). The study enrolled 110 patients with type 2 diabetes mellitus (T2DM) and 70 age-matched healthy controls, aged 32–70 years. Patients were stratified into four age groups: <40 years (n = 23), 40–49.9 years (n = 36), 50–59.9 years (n = 24), and ≥60 years (n = 27).

Sample Collection and Laboratory Analyses

Fasting venous blood samples (5 mL) were collected and processed for biochemical analysis. Plasma orexin-A and cathepsin-D concentrations were determined using commercially available enzyme-linked immunosorbent assay (ELISA) kits (MyBioSource, USA). Glycated hemoglobin (HbA1c) was measured by high-performance liquid chromatography (HPLC) using the VARIANT™ 2 TURBO system (Bio-Rad, USA). Serum insulin and C-peptide levels were quantified by electrochemiluminescence immunoassay on a COBAS e411 analyzer (Roche Diagnostics, Germany). Fasting plasma glucose and lipid profiles were assessed by enzymatic colorimetric methods using the COBAS INTEGRA 400 analyzer (Roche Diagnostics, Germany).

Indices of Insulin Resistance

Insulin resistance was estimated using the homeostasis model assessment of insulin resistance (HOMA-IR), calculated as:

$$\text{HOMA-IR} = \text{fasting insulin } (\mu\text{IU/mL}) \times \text{fasting glucose (mg/dL)} / 405.$$

Statistical Analysis

Data were analyzed using SPSS version 25 (IBM Corp., Armonk, NY, USA). Normality was assessed with the Kolmogorov–Smirnov test. Non-normally distributed data are presented as median (minimum–maximum). Group comparisons were performed using the Mann–Whitney U test for two groups and the Kruskal–Wallis test for multiple groups. Correlations were evaluated using Spearman's rank correlation coefficient. Multiple regression analysis was conducted to identify independent predictors of insulin resistance. A p-value < 0.05 was considered statistically significant.

ISSN 3063-8186 (online), https://ijhsm.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

Results

Baseline Characteristics

The patient group comprised 68 males (61.8%) and 42 females (38.2%), with a comparable distribution among the controls (65.7% males and 34.3% females). There were no significant differences in age or sex distribution between patients and controls ($p > 0.05$).

Age-Related Changes in Orexin-A

A progressive, age-related decline in orexin-A levels was observed (Table 1). In patients aged <40 years, the median orexin-A concentration was 177 pg/mL (range: 60–289), decreasing to 100 pg/mL (77–160) in the 40–49.9 year group, 77 pg/mL (53–100) in the 50–59.9 year group, and reaching a nadir of 54 pg/mL (13–93) in those aged ≥60 years ($p = 0.001$). This pattern corresponds to an overall 69% reduction across the age groups.

Age-Related Changes in Cathepsin-D

Cathepsin-D levels showed a significant age-related increase (Table 1). Concentrations rose from a median of 16 pg/mL (range: 4–36) in patients aged <40 years to 20.5 pg/mL (5–36) in the 40–49.9 year group, 25.5 pg/mL (7–38) in the 50–59.9 year group, and 29 pg/mL (5–38) in those aged ≥60 years ($p = 0.005$), representing an overall 81% increase across the age groups.

Table 1: Age-Related Changes in Biomarkers in T2DM Patients

Age Group	n	Orexin-A (pg/ml)	Cathepsin-D (pg/ml)	Insulin (µU/ml)	C-peptide (ng/ml)	HOMA-IR
<40 years	23	177 (60-289)	16 (4-36)	15.6 (3.1-41.6)	3.6 (1.2-6.6)	3.8 (0.7-10.2)
40-49.9 years	36	100 (77-160)*	20.5 (5-36)*	23.2 (3.1-66.2)	4.1 (1.2-8.6)	5.7 (0.7-16.3)
50-59.9 years	24	77 (53-100)**	25.5 (7-38)**	24.9 (9.6-41.7)	4.8 (1.9-8.6)*	6.1 (2.4-10.3)*
≥60 years	27	54 (13-93)***	29 (5-38)***	24.2 (10.2-50.2)	4.3 (2.5-8.6)*	5.9 (2.5-12.3)**
p-value		0.001	0.005	0.076	0.024	0.001

Data presented as median (min-max). *p<0.05, **p<0.01, ***p<0.001 compared to <40 years group.

Correlations with Age and Metabolic Parameters

Table 2 summarizes the correlations between the three biomarkers (Orexin-A, Cathepsin-D and HOMA-IR) and key metabolic parameters in patients with type 2 diabetes mellitus (T2DM). There is a strong negative relationship between age and orexin-A ($r = -0.84$, $p = 0.01$) and this indicates that the level of Orexin-A in the old is usually very low. It also correlates negatively with body mass index (BMI, $r = -0.38$), HbA1c (-0.41), insulin (-0.29), C-peptide (-0.26), triglycerides (TG, -0.31), and low-density lipoprotein (LDL, -0.27), which means that the lower the amount of Orexin-A, the higher the adiposity, the worse the glycemic control, and the worse the dyslipidemia. It is only significant with fasting blood sugar (FBS) with no significant correlation with high-density lipoprotein (HDL). These findings give credence to the preventive role of Orexin-A, which decreases with old age, insulin resistance, and poor metabolic characteristics.

Most of the indices have a positive relation with cathepsin-D such as age (0.4), BMI (0.42), HbA1c (0.88), FBS (0.88), insulin (0.63), C-peptide (0.63), TG (0.44), and LDL (0.25); furthermore, there is no significant relation with HDL. This tendency suggests that high Cathepsin-D concentrations correlate with hyperglycemia, insulin secretion, and dyslipidemia that could be the symptoms of inflammation or metabolic stress in type 2 diabetes. The measure of insulin resistance, HOMA-IR, does not have any correlation with HDL, but has a significant positive association with age (0.22), BMI (0.39), HbA1c (0.67), FBS (0.82), C-peptide (0.72) and TG (0.38). It is also borderline related with LDL (0.18, $p = 0.058$). The correlations confirm the role of HOMA-IR as an insulin resistance measure because they indicate that elevated HOMA-IR levels are correlated with poorer glycemic control, more adiposity, and lipid dysregulation.

ISSN 3063-8186 (online), https://ijhsm.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

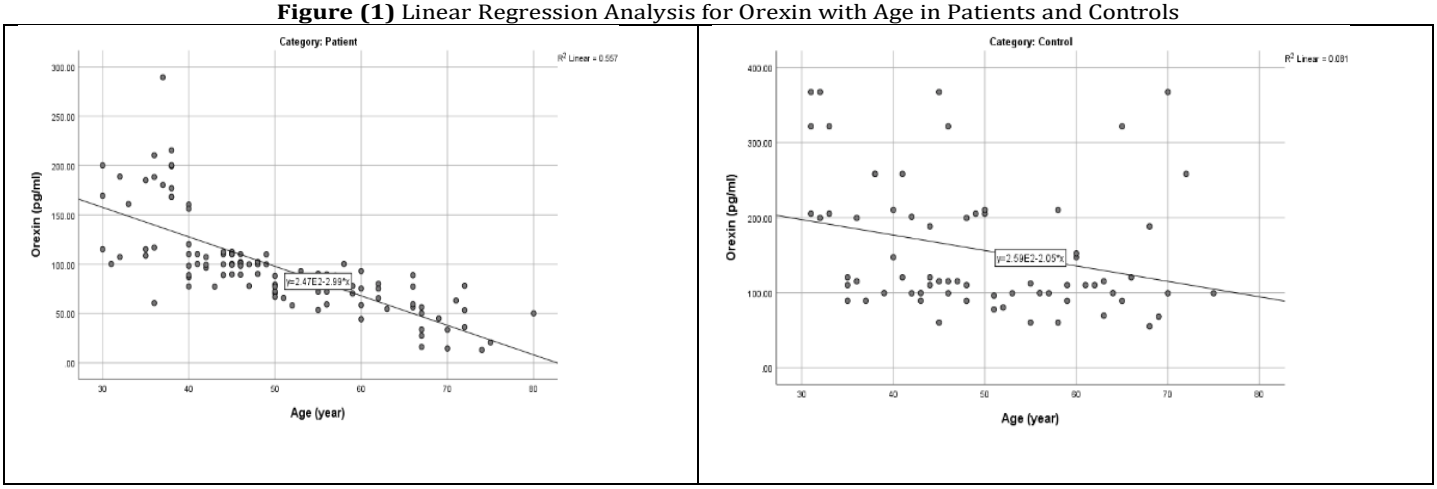
Table 2: Correlation Analysis of Biomarkers with Metabolic Parameters in T2DM Patients

Parameters	Orexin-A		Cathepsin-D		HOMA-IR	
	R	P	R	P	r	P
Age	-0.84	0.01	0.4	0.02	0.22	0.001
BMI	-0.38	0.01	0.42	0.01	0.39	0.002
HbA1c%	-0.41	0.05	0.88	0.01	0.67	0.001
FBS (mg/dl)	-0.83	0.387	0.88	0.05	0.82	0.001
Insulin (µU/ml)	-0.29	0.002	0.63	0.01	-	-
C-peptide (ng/ml)	-0.26	0.006	0.63	0.05	0.72	0.001
TG (mg/dl)	-0.31	0.001	0.44	0.01	0.38	0.005
HDL (mg/dl)	0.12	0.179	0.1	0.256	0.15	0.1
LDL (mg/dl)	-0.27	0.004	0.25	0.008	0.18	0.058

r = Spearman's correlation coefficient

The association between age and Orexin-A levels is shown in the scatter plot (figure 1), which shows that patients with type 2 diabetic mellitus (T2DM) have a noticeably steeper drop than healthy controls. Orexin-A declines significantly with age in T2DM patients (r = –0.84), but the negative slope is less pronounced in the control group (r = –0.33). This suggests that Orexin-A is more substantially suppressed by aging in diabetics than in healthy controls.

Figure (1) Linear Regression Analysis for Orexin with Age in Patients and Controls



Traditional Metabolic Parameters by Age

Table 3 shows variations in traditional markers with age. Key metabolic markers for patients with type 2 diabetes mellitus in four age groups are compared in this table. The lipid profile and glycemic control clearly deteriorate with aging. The median HbA1c increases gradually with age, from 8.9% in those under 40 to 11.2% in those over 60 (p = 0.005), suggesting progressively worse long-term glucose management. Age differences in fasting blood sugar (FBS) are not statistically significant (p = 0.387). Low-density lipoprotein (LDL), total cholesterol (TC), and triglycerides (TG) all rise dramatically with age. For example, TG increased from a median of 145 mg/dl (<40 years) to 195 mg/dl (≥60 years; p = 0.001). Likewise, there are notable increases in TC and LDL (p = 0.001).

High-density lipoprotein (HDL), on the other hand, dramatically drops from a median of 42 mg/dl in the youngest group to 32 mg/dl in the oldest (p = 0.001). Overall, these results show that older T2DM patients had more atherogenic lipid profiles, which are defined by higher TG, TC, LDL, and lower HDL levels, as well as poorer long-term glycemic control.

Table 3: Traditional Metabolic Parameters Across Age Groups in T2DM Patients

Age Group	**HbA1c (%)**	**FBS (mg/dl)**	**TG (mg/dl)**	**TC (mg/dl)**	**HDL (mg/dl)**	**LDL (mg/dl)**
<40 years	8.9 (5.2-11.8)	178 (70-380)	145 (84-310)	185 (98-250)	42 (28-59)	115 (36-180)
40-49.9 years	9.8 (6.0-12.0)	195 (85-420)	168 (90-385)	198 (110-260)	38 (26-55)	125 (45-190)

ISSN 3063-8186 (online), https://ijhsm.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

50-59.9 years	10.5 (6.5-12.6)*	210 (90-460)	185 (95-431)*	210 (125-271)*	35 (24-50)*	135 (55-201)*
≥60 years	11.2 (7.0-12.6)**	205 (95-440)	195 (100-420)**	215 (130-265)**	32 (24-48)**	140 (60-195)**
p-value	0.005	0.387	0.001	0.001	0.001	0.001

Data presented as median (min-max). *p<0.05, **p<0.01 compared to <40 years group.

Multiple Regression Analysis

Independent predictors of HOMA-IR were found using multiple regression analysis (Table 4). Independent predictors of insulin resistance as determined by HOMA-IR are found in this investigation. Age (β = 0.18, p = 0.02), BMI (β = 0.35, p < 0.001), and Cathepsin-D (β = 0.31, p = 0.001) are all significant positive predictors, suggesting that increased insulin resistance is independently linked to older age, higher BMI, and raised Cathepsin-D levels. Orexin-A, on the other hand, exhibits a significant negative correlation (β = −0.24, p = 0.005), indicating that higher levels of Orexin-A are protective against insulin resistance. The model explains 52% of the variance in HOMA-IR (R^2 = 0.52, p < 0.001), indicating that insulin resistance in type 2 diabetes is influenced by both established risk variables (age, BMI) and novel biomarkers (Cathepsin-D, Orexin-A).

Table 4: Multiple Regression Analysis for Predictors of HOMA-IR

Variable	**β coefficient**	**Standard Error**	**p-value**	**95% CI**
Age	0.18	0.08	0.02	0.02-0.34
BMI	0.35	0.09	<0.001	0.17-0.53
Orexin-A	-0.24	0.08	0.005	-0.32
Cathepsin-D	0.31	0.09	0.001	0.13-0.49

Model R^2 = 0.52, p<0.001

BMI-Stratified Analysis

In the case of stratification by BMI, considerable differences were noted (Figure 4):

Disagreement in Biomarkers by BMI.

A number of biomarkers have significant differences when patients are grouped based on the BMI (normal ≤24.9 vs. abnormal ≥25). The median Orexin-A (84 pg/ml vs. 110 pg/ml, p = 0.001), Cathepsin-D (26 pg/ml vs. 16 pg/ml, p = 0.02), IAPP (26.6 pg/ml vs. 9.6 pg/ ml, p =0.002), insulin(23.2 ug/ml vs.15.4 ug/ml, p =0.001), and C-peptide(4 No significant difference in the level of GIP is observed (p = 0.7). These findings support the relationship between obesity and progressive metabolic risk because the biomarker patterns of increased insulin secretion and metabolic stress-reduced Orexin-A, elevated Cathepsin-D, IAPP, insulin, and C-peptide were found in overweight or obese T2DM patients.

Table (5) The Differences of Orexin, GIP, Cathepsin-D, IAPP, Insulin, and C-Peptide Between Patients according to BMI.

Biomarker		Orexin (pg/ml)	Cathepsin-D (pg/ml)	Insulin um/ml	C-Peptide Ng/ml
N		Normal BMI=38 Abnormal BM =72			
Normal BMI	Median	110	16	15.4	3.4
≤ 24.9	Min.-Max.	(27_289)	(4_36)	(3.1_41.6)	(1.2_6.7)

ISSN 3063-8186 (online), https://ijhsm.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

	P-value	0.001	0.02	0.001	0.005
Ab normal BMI	Median	84	26	23.2	4.8
≥25.0	Min.-Max.	(13_200)	(6_38)	(3.1_66.2)	(1.9_8.6)

Discussion

This pioneering work provides the first extensive analysis of the age-related changes in orexin-A and cathepsin-D in type 2 diabetes mellitus (T2DM) patients, which reveals a systematic deterioration of cellular quality-control mechanisms and hypothalamic activity accelerating with age. We discovered alarming 69 percent reduction in orexin-A and a 81 percent increase in cathepsin-D that was across the age brackets giving us much needed information on the progressive metabolic impairment that is described in older diabetics.

The pivotal part of Orexin deficiency in the decrease of the metabolism.

Our findings indicate that the age reduction in orexin-A that is typically observed in healthy aging population is significantly overcome by the age reduction in T2DM patients [13], [14]. This fact is demonstrated by the fact that the negative correlation between orexin and age is significantly higher in patients ($r = -0.84$, $p = 0.01$) compared to controls ($r = -0.33$, $p = 0.004$), which means that the death of hypothalamic neurons is facilitated by diabetes-specific mechanisms. This progressive degradation is probably due to a synergistic interaction of aging and diabetic related variables, which include oxidative stress, chronic inflammation specifically directed at the lateral hypothalamus, and neurotoxicity due to the chronic hyperglycemia. [15], [16].

The mechanistic consequences of orixin insufficiency extend beyond the loss of neurons. The negative relationship between orexin and insulin resistance ($r = -0.26$, $p = 0.005$) can be confirmed by experimental evidence of the complex insulin-sensitizing actions of orexin. They involve augmentation of hepatic insulin sensitivity, amplification of glucose uptake by GLUT4 translocation, alteration of the work of the autonomic nervous system, and mediating of the inflammatory processes [17][18][19][20]. All these findings suggest that age-related orexin deficit is the cause above all, of metabolic degradation, not merely an outcome, which leads to vicious circle of hypothalamic dysfunction slowly increasing peripheral insulin resistance.

Biomarker Cellular Dysfunction Cathepsin-D.

Type 2 diabetes is highly indicated to experience severe lysosomal dysfunction and failure in cellular quality control with the growing age-related elevated level of cathepsin-D. Cathepsin-D maintains cellular proteostasis by promoting the degradation of misfolded proteins through the autophagy-mediated mechanism in physiological conditions [21]. Nonetheless, our finding that the cathepsin-D levels of T2DM patients were nearly fivefold higher than the controls do indicate that the normal breakdown pathways are congested. This malfunction leads to the extracellular release of cathepsin-D that actively facilitates insulin resistance and inflammation [22], [23].

Importantly, the positive relationship between cathepsin-D and glycemic indices (fasting blood sugar: $r = 0.88$, $p = 0.05$; HbA1c: $r = 0.88$, $p = 0.01$) was quite high, which demonstrates that lysosomal impairment is mainly predetermined by chronic hyperglycemia. This observation is in line with the information that the release of cathepsin is caused by the glucose-induced lysosomal membrane permeabilization [24]. The role of cathepsin-D as a biomarker of duration and severity of metabolic stress is justified by the simultaneous increase in levels with age which is a cumulative damage of cells and progressive loss of metabolic capacity.

The Novel Orexin-Cathepsin-D Pathophysiological Axis.

Among the most interesting results of our study is the inverse correlation between orexin and cathepsin-D ($r = -0.36$, $p = 0.002$), where the relationship has never been reported previously, which outlines a previously unrecognised pathophysiological relationship between the malfunctioning of the central hypothalamic and the cellular response to stress. The following relationship might be due to several mechanisms that are interconnected:

Due to the demonstrated neuroprotective activity of orexin, it may be transferred to peripheral tissues, reducing cellular stress and the liberation of cathepsin-D [25]. Second, the deficiency in orexin can lead to an imbalance in the autonomic nervous system that can aggravate the lysosomal dysfunction and disrupt the homeostasis of peripheral tissues [26]. Third,

orexin deficiency facilitates systemic inflammation to increase cathepsin-D, which indicates that it is possible to use the proposed axis to explain the peripheral metabolic damage caused by hypothalamic dysfunction and suggest new pathophysiological models of age-related diabetes progression.

Conclusions

According to this study, major hypothalamic impairment, which is shown by a reduction of orexin levels by 69 percent, and impaired cellular quality control, which is demonstrated by an increase of cathepsin-D levels by 81 percent, is associated with aging in patients with type 2 diabetic mellitus (T2DM). The connection between both changes and the worsening insulin resistance is evident. These processes are increased in diabetes-specific acceleration through the large differences between patient and control age-related patterns of biomarkers.

These findings imply that older diabetic individuals should be treated in a specific way and provide solid proof of age-related pathophysiological mechanisms that transcend the traditional glycemic malfunction. In addition, the finding of orexin-cathepsin-D axis as a new pathway between peripheral metabolic stress and central hypothalamic dysfunction demonstrates the importance of hypothalamic preservation in diabetes treatment and provides new therapeutic possibilities.

Acknowledgments

We would like to thank all the people who generously participated in this research and those who worked in the Faiha Specialized Diabetes, Endocrine and Metabolism Center as well.

References

1. M. A. B. Khan, M. J. Hashim, J. K. King, R. D. Govender, H. Mustafa, and J. Al Kaabi, "Epidemiology of type 2 diabetes–global burden of disease and forecasted trends," J. Epidemiol. Glob. Health, vol. 10, no. 1, pp. 107-111, 2020.
2. H. Sun, P. Saeedi, S. Karuranga, et al., "IDF Diabetes Atlas: Global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045," Diabetes Res. Clin. Pract., vol. 183, pp. 109119, 2022.
3. S. Bellary, I. Kyrou, J. E. Brown, and C. J. Bailey, "Type 2 diabetes mellitus in older adults: clinical considerations and management," Nat. Rev. Endocrinol., vol. 17, no. 9, pp. 534-548, 2021.
4. S. C. Schriever, D. G. Kabra, K. Pfuhlmann, et al., "Type 2 diabetes risk gene Dusp8 regulates hypothalamic Jnk signaling and insulin sensitivity," J. Clin. Invest., vol. 130, no. 11, pp. 6093-6108, 2020.
5. R. Herman, N. A. Kravos, M. Jensterle, A. Janež, and V. Dolžan, "Metformin and insulin resistance: a review of the underlying mechanisms," Int. J. Mol. Sci., vol. 23, no. 3, pp. 1264, 2022.
6. X. Liu, R. Yang, W. Bai, et al., "Exploring the role of orexin B-sirtuin 1-HIF-1α in diabetes-mellitus induced vascular endothelial dysfunction," Life Sci., vol. 254, pp. 117041, 2020.
7. R. Van Drunen and K. Eckel-Mahan, "Circadian rhythms of the hypothalamus: from function to physiology," Clocks Sleep, vol. 3, no. 1, pp. 189-226, 2021.
8. J. M. Erichsen, C. B. Calva, L. P. Reagan, and J. R. Fadel, "Intranasal insulin and orexins to treat age-related cognitive decline," Physiol. Behav., vol. 234, pp. 113370, 2021.
9. V. Stoka, V. Turk, and B. Turk, "Lysosomal cathepsins and their regulation in aging and neurodegeneration," Ageing Res. Rev., vol. 32, pp. 22-37, 2016.
10. L. Ding, G. H. Goossens, Y. Oligschlaeger, et al., "Plasma cathepsin D activity is negatively associated with hepatic insulin sensitivity in overweight and obese humans," Diabetologia, vol. 63, pp. 374-384, 2020.
11. M. Kher, S. Beri, H. S. Rehan, A. Prakash, and L. K. Gupta, "Effect of metformin and insulin combination on monocyte chemoattractant protein-1 and cathepsin-D in type 2 diabetes mellitus," Diabetes Metab. Syndr., vol. 14, no. 6, pp. 1703-1710, 2020.
12. L. Liu, B. Chen, X. Zhang, L. Tan, and D. W. Wang, "Increased cathepsin D correlates with clinical parameters in newly diagnosed type 2 diabetes," Dis. Markers, vol. 2017, pp. 5286408, 2017.
13. H. Tsuneki, K. Honda, Y. Sekine, et al., "C-terminal peptide of preproorexin enhances brain-derived neurotrophic factor expression in rat cerebrocortical cells," Eur. J. Pharmacol., vol. 964, pp. 176306, 2024.
14. X. Chen, W. Yang, Y. Xue, et al., "Orexin increases the neuronal excitability of several brain areas associated with arousal maintenance," J. Neurochem., vol. 168, no. 9, pp. 2379-2390, 2024.
15. C. H. Sadiq, R. H. Hussein, and I. M. Maulood, "Relationship between orexin-a and insulin resistance in patients with type 2 diabetes mellitus," Iraqi J. Sci., vol. 62, no. 3, pp. 779-786, 2021.
16. Y. Hao, H. Yuan, P. Fang, et al., "Plasma orexin-A level associated with physical activity in obese people," Eat. Weight Disord., vol. 22, pp. 69-77, 2017.
17. M. Zarifkar, S. Noshad, M. Shahriari, et al., "Inverse association of peripheral orexin-A with insulin resistance in type 2 diabetes mellitus," Rev. Diabet. Stud., vol. 14, no. 2-3, pp. 301-307, 2017.
18. E. Yilmaz, O. Celik, N. Celik, et al., "Maternal and fetal serum orexin-A levels in gestational diabetes mellitus," J. Obstet. Gynaecol. Res., vol. 39, no. 1, pp. 139-145, 2013.
19. E. Dufoo-Hurtado, A. Wall-Medrano, and R. Campos-Vega, "Naturally-derived chronobiotics in chrononutrition," Trends Food Sci. Technol., vol. 95, pp. 173-182, 2020.
20. D. Pocevičiūtė, B. Roth, B. Ohlsson, and M. Wennström, "Okinawa-Based Nordic Diet Decreases Plasma Levels of IAPP and IgA against IAPP Oligomers in Type 2 Diabetes Patients," Int. J. Mol. Sci., vol. 25, no. 14, pp. 7665, 2024.
21. L. Ding, T. J. I. De Munck, Y. Oligschlaeger, et al., "Myosteatosis in NAFLD patients correlates with plasma Cathepsin D," Biomol. Concepts, vol. 12, no. 1, pp. 27-35, 2021.
22. S. Reddy, A. Amutha, R. Rajalakshmi, et al., "Association of increased levels of MCP-1 and cathepsin-D in young onset

type 2 diabetes patients with severity of diabetic retinopathy," J. Diabetes Complications, vol. 31, no. 5, pp. 804-809, 2017.
23. J. Wang, J. Du, X. Ge, et al., "Circulating Ism1 reduces the risk of Type 2 diabetes but not diabetes-associated NAFLD," Front. Endocrinol., vol. 13, pp. 890332, 2022.
24. J. Ahmad, M. Zubair, A. Malik, M. A. Siddiqui, and S. K. Wangnoo, "Cathepsin-D, adiponectin, TNF-α, IL-6 and hsCRP plasma levels in subjects with diabetic foot," The Foot, vol. 22, no. 3, pp. 194-199, 2012.
25. P. Khurana, T. Yadati, S. Goyal, et al., "Inhibiting extracellular cathepsin D reduces hepatic steatosis in Sprague–Dawley rats," Biomolecules, vol. 9, no. 5, pp. 171, 2019.
26. L. Ding, T. Houben, Y. Oligschlaeger, et al., "Plasma cathepsin D activity rather than levels correlates with metabolic parameters of type 2 diabetes in male individuals," Front. Endocrinol., vol. 11, pp. 575070, 2020.
27. J. A. Rodriguez-Navarro, S. Kaushik, H. Koga, et al., "Inhibitory effect of dietary lipids on chaperone-mediated autophagy," Proc. Natl. Acad. Sci. USA, vol. 109, pp. E705-E714, 2022.
28. T. Min and S. C. Bain, "The role of tirzepatide, dual GIP and GLP-1 receptor agonist, in the management of type 2 diabetes," Diabetes Ther., vol. 12, pp. 143-157, 2021.
29. C. N. Boyle, T. A. Lutz, and C. Le Foll, "Amylin–Its role in the homeostatic and hedonic control of eating and recent developments of amylin analogs," Mol. Metab., vol. 8, pp. 203-210, 2018.
30. I. Gonzalez-Mariscal, S. M. Krzysik-Walker, M. E. Doyle, et al., "Human CB1 receptor isoforms in hepatocytes and β-cells regulate metabolism," Sci. Rep., vol. 6, no. 1, pp. 33302, 2016.

ISSN 3063-8186 (online), https://ijhsm.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo