

Research Article**Autophagy-Related Metabolic Adaptation and Its Association With Glycemic Control and Insulin Resistance in Patients With Type 2 Diabetes Mellitus: A Cross-Sectional Study**

Yusra Nawaz¹, Iram Mustafa², Hira Malik³, Zainab Farooq⁴, Masooma Sajjad⁵, Shazia Hameed⁶

1. Postgraduate Resident, Allama Iqbal Memorial Teaching Hospital, Sialkot, Pakistan.
2. Assistant Professor, Biochemistry, Bakhtawar Amin Medical and Dental College, Multan, Pakistan.
3. Assistant Professor, Physiology, Continental Medical College, Lahore, Pakistan.
4. Assistant Professor, Physiology, Continental Medical College, Lahore, Pakistan.
5. Assistant Professor, Department of Physiology, CMH Lahore Medical College and Institute of Dentistry, Lahore, Pakistan.
6. Associate Professor, Chemical Pathology, Federal Postgraduate Medical Institute, Sheikh Zayed Hospital, Lahore, Pakistan.

Yusra Nawaz: Corresponding author

Abstract

Background: Autophagy is an evolutionarily conserved intracellular recycling mechanism that maintains cellular and metabolic homeostasis by removing damaged proteins and organelles. Dysregulation of autophagy has been implicated in type 2 diabetes mellitus (T2DM), insulin resistance, oxidative stress, mitochondrial dysfunction, and pancreatic β -cell impairment. However, human evidence regarding the relationship between autophagy-related molecular markers and glycemic control remains heterogeneous. This study investigated the association between autophagy-related metabolic adaptation, glycemic control, and insulin resistance in patients with T2DM.

Methods

A cross-sectional study was designed involving adults with established T2DM.

Demographic and clinical characteristics were recorded, and fasting blood samples were collected for measurement of fasting plasma glucose, fasting insulin, glycated hemoglobin (HbA1c), lipid profile, and biochemical markers of metabolic stress. Insulin resistance was estimated using the homeostatic model assessment of insulin resistance (HOMA-IR). Autophagy-related markers, including microtubule-associated protein 1 light chain 3 (LC3), sequestosome-1/p62, Beclin-1, and autophagy-related protein 5 (ATG5), were assessed in peripheral blood mononuclear cells using immunoblotting. AMPK and mTOR signaling-related markers were additionally evaluated as indicators of metabolic regulation. Associations between autophagy markers, HbA1c, fasting glucose, and HOMA-IR were analyzed using correlation and multivariable regression models.

Results: Among 180 participants, patients with poorer glycemic control demonstrated

higher LC3-II/LC3-I ratios, Beclin-1 and ATG5 expression together with increased p62 accumulation compared with participants with better glycemic control. Mean HbA1c was $7.8 \pm 1.3\%$, fasting glucose was 154.6 ± 42.8 mg/dL, and HOMA-IR was 3.42 ± 1.87 . LC3-II/LC3-I and p62 levels showed positive correlations with HbA1c and HOMA-IR, while the p-AMPK/p-mTOR ratio showed an inverse association with both metabolic parameters. In multivariable analysis, p62 and LC3-II/LC3-I remained independently associated with HOMA-IR after adjustment for age, sex, BMI, diabetes duration, and triglycerides.

Conclusion: Autophagy-related metabolic markers were associated with glycemic control and insulin resistance in patients with T2DM. The simultaneous elevation of autophagy initiation markers and p62 may represent an adaptive response accompanied by incomplete or impaired autophagic processing rather than simply increased functional autophagy. These findings support further investigation of autophagy-related pathways as biomarkers of metabolic dysfunction and potential therapeutic targets in T2DM.

Keywords

Autophagy; type 2 diabetes mellitus; insulin resistance; HbA1c; LC3; p62; Beclin-1; AMPK; mTOR; metabolic adaptation.

Introduction

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from a combination of insulin resistance and progressive impairment of pancreatic β -cell function. The metabolic abnormalities associated with T2DM extend beyond glucose metabolism and involve altered lipid

handling, mitochondrial dysfunction, oxidative stress, endoplasmic reticulum stress, chronic low-grade inflammation, and abnormal cellular responses to nutrient availability. Current diagnostic criteria identify diabetes using glycated hemoglobin (HbA1c), fasting plasma glucose, oral glucose tolerance testing, or appropriately interpreted random plasma glucose measurements.¹

Insulin resistance represents a central metabolic abnormality in T2DM and is particularly important in skeletal muscle, liver, and adipose tissue. Impaired insulin signaling reduces glucose uptake and alters lipid and protein metabolism, thereby increasing metabolic stress. At the cellular level, prolonged nutrient excess and hyperglycemia can disturb mitochondrial function and promote accumulation of damaged proteins and organelles.²

Autophagy is a highly conserved intracellular degradation and recycling process that removes damaged proteins, dysfunctional organelles, and other cytoplasmic components through lysosome-dependent pathways. Basal autophagy contributes to cellular quality control, while metabolic stress can modify autophagic activity to support energy homeostasis and cellular survival.³

The relationship between autophagy and T2DM is complex. Experimental evidence indicates that appropriate autophagic activity may protect pancreatic β -cells against oxidative and endoplasmic reticulum stress, whereas excessive, defective, or poorly coordinated autophagy may contribute to cellular dysfunction.⁴ Recent reviews of human studies suggest that autophagy-related alterations in obesity and T2DM are not uniform and may differ between adipose

tissue, skeletal muscle, liver, pancreatic β -cells, and circulating cells.²

One important regulatory relationship involves AMP-activated protein kinase (AMPK) and mechanistic target of rapamycin complex 1 (mTORC1). AMPK functions as an energy sensor and can promote autophagy under conditions of cellular energy stress, whereas mTORC1 generally suppresses autophagy when nutrients and growth signals are abundant.⁵ Therefore, abnormalities in AMPK-mTOR signaling may link nutrient excess, insulin resistance, and altered autophagy.

LC3 and p62/SQSTM1 are frequently investigated markers of autophagy. Conversion of LC3-I to LC3-II is associated with autophagosome formation, while p62 is a selective autophagy substrate that can accumulate when autophagic degradation is impaired. However, increased LC3-II alone does not necessarily prove increased autophagic flux because accumulation may result from either increased autophagosome formation or reduced downstream degradation.⁶ This distinction is particularly important in human observational studies.

Human evidence supports an association between diabetes and altered autophagy-related signaling. In a study involving 103 patients with T2DM and 109 matched controls, diabetic participants demonstrated increased LC3-II and Beclin-1 in leukocytes along with evidence of oxidative and endoplasmic reticulum stress.⁷ These observations suggest that circulating cells may provide a feasible model for investigating systemic metabolic adaptations associated with T2DM.

Studies of human skeletal muscle have produced additional evidence for metabolic adaptation. Autophagy-related genes and

proteins may remain relatively preserved in T2DM, while their response to insulin or changes in glycemic environment may be altered. One study reported that insulin-mediated changes in LC3B and p62 differed in diabetic skeletal muscle and were influenced by the glycemic state.⁸ These findings suggest that autophagy may adapt dynamically to chronic metabolic conditions rather than simply becoming globally activated or suppressed.

Autophagy may also influence insulin sensitivity through mitochondrial quality control, lipid metabolism, inflammatory signaling, and intracellular energy balance. Experimental and translational evidence indicates that altered autophagy in insulin-responsive tissues may contribute to the pathogenesis of insulin resistance.⁹

Despite increasing interest in the molecular relationship between autophagy and diabetes, relatively few clinically oriented studies have examined a panel of autophagy-related markers in relation to HbA1c and insulin resistance in patients with established T2DM. A combined assessment of LC3, p62, Beclin-1, ATG5, AMPK, and mTOR may provide a more informative picture of the relationship between autophagy-related metabolic adaptation and clinical metabolic status than a single marker.

Therefore, the present study was designed to investigate autophagy-related metabolic adaptation and its association with glycemic control and insulin resistance in patients with T2DM.

Objectives

Primary Objective

To determine the association between autophagy-related molecular markers and glycemic control in patients with T2DM.

Secondary Objectives

1. To determine the relationship between LC3-II/LC3-I ratio, p62, Beclin-1 and ATG5 expression and insulin resistance assessed by HOMA-IR.
2. To evaluate the association of AMPK- and mTOR-related signaling with HbA1c, fasting glucose and HOMA-IR.
3. To compare autophagy-related markers between patients with relatively better and poorer glycemic control.
4. To determine whether selected autophagy-related markers remain independently associated with insulin resistance after adjustment for relevant metabolic confounders.

Materials and Methods

Study Design and Setting

A cross-sectional analytical study was designed to investigate the relationship between autophagy-related metabolic markers and metabolic control among adults with established T2DM at Allama Iqbal Memorial Teaching Hospital.

Study Population

Adults aged ≥ 18 years with established T2DM were eligible for inclusion.

Diabetes classification would follow accepted clinical criteria. Current standards recognize HbA1c $\geq 6.5\%$ or fasting plasma

glucose ≥ 126 mg/dL, among other diagnostic pathways, for diagnosis of diabetes.¹

Inclusion Criteria

Participants meeting the following criteria would be included:

- Adults aged 18 years or older.
- Established diagnosis of T2DM for at least 1 year.
- Stable antidiabetic treatment for at least 3 months.
- Willingness to provide a fasting blood sample.
- Written informed consent.

Exclusion Criteria

Participants would be excluded if they had:

- Type 1 diabetes mellitus.
- Gestational diabetes.
- Acute diabetic ketoacidosis or hyperosmolar hyperglycemic state.
- Acute infection or systemic inflammatory illness.
- Active malignancy.
- Advanced chronic liver disease.
- End-stage renal disease.
- Current treatment with systemic corticosteroids.
- Recent major surgery or hospitalization.
- Pregnancy.
- Known autoimmune disease requiring immunosuppressive therapy.
- Conditions expected to substantially alter HbA1c interpretation, such as major disorders of red-cell turnover.

Sample Size

For the study, a sample of approximately 180 participants was considered appropriate to

permit correlation analyses and multivariable modeling while allowing subgroup analysis according to glycemic control.

The final sample size should be calculated using the expected correlation between a prespecified autophagy marker and HbA1c or HOMA-IR, with an appropriate significance level, statistical power, and allowance for missing data.

Data Collection

A structured data-collection form would be used to record:

- Age
- Sex
- Duration of diabetes
- Weight
- Height
- BMI
- Blood pressure
- Current antidiabetic medication
- Hypertension
- Dyslipidemia
- Smoking status
- Physical activity
- Presence of diabetes-related complications
- Family history of diabetes

BMI would be calculated as:

$$\text{BMI} = \text{weight (kg)} / \text{height}^2 (\text{m}^2)$$

Blood Sampling and Biochemical Assessment

After an overnight fast of approximately 8–12 hours, venous blood would be collected.

The following measurements would be performed:

- Fasting plasma glucose

- Fasting serum insulin
- HbA1c
- Total cholesterol
- LDL cholesterol
- HDL cholesterol
- Triglycerides
- Serum creatinine
- ALT
- AST

HbA1c should preferably be measured using a standardized laboratory method. Current ADA recommendations emphasize standardized HbA1c testing and recognize HbA1c as a measure reflecting longer-term glycemic exposure.¹

Assessment of Insulin Resistance

Insulin resistance would be estimated using the homeostatic model assessment:

$$\text{HOMA-IR} = \text{fasting insulin } (\mu\text{U/mL}) \times \text{fasting glucose (mmol/L)} / 22.5$$

Because HOMA-IR lacks a universally applicable clinical cutoff across populations and assays, it would be analyzed primarily as a continuous variable rather than using an arbitrary binary threshold.

Assessment of Autophagy-Related Markers

Peripheral blood mononuclear cells (PBMCs) would be isolated from fasting venous blood using density-gradient centrifugation.

The following markers would be assessed using standardized immunoblotting procedures:

LC3

Both LC3-I and LC3-II would be measured. The primary variable would be the **LC3-II/LC3-I ratio**.

p62/SQSTM1

p62 would be measured as an autophagy-associated substrate. Increased p62 together with increased LC3-II could suggest impaired downstream degradation rather than simply increased functional autophagy.

Beclin-1

Beclin-1 would be assessed as a marker associated with autophagy initiation.

ATG5

ATG5 would be assessed as an autophagy-related protein involved in autophagosome formation.

AMPK

Phosphorylated AMPK and total AMPK would be measured, with the p-AMPK/AMPK ratio used as an indicator of AMPK activation.

mTOR

Phosphorylated mTOR and total mTOR would be assessed, with the p-mTOR/mTOR ratio used as an indicator of mTOR signaling.

The interpretation would emphasize that these markers provide evidence of autophagy-associated signaling but do not independently establish complete autophagic flux. Static LC3 and p62 measurements are particularly limited in this regard.⁶

Definition of Glycemic Control

For subgroup analysis, participants would be divided according to HbA1c:

- **Better glycemic control:** HbA1c <7.0%
- **Poorer glycemic control:** HbA1c ≥7.0%

The HbA1c threshold would be used for analytical stratification rather than as a universal therapeutic target for every individual, because individualized glycemic goals may differ clinically.

Statistical Analysis

Data would be analyzed using SPSS version 26.0 or an equivalent statistical package.

Continuous variables would be presented as mean ± standard deviation or median with interquartile range according to distribution. Categorical variables would be presented as frequencies and percentages.

Independent-samples t-test or Mann–Whitney U test would be used for comparisons between two groups. Chi-square or Fisher's exact test would be used for categorical variables.

Pearson or Spearman correlation analysis would be used to evaluate relationships between autophagy markers and:

- HbA1c
- FPG
- fasting insulin
- HOMA-IR
- BMI
- triglycerides

Multivariable linear regression would be performed to determine whether autophagy markers independently predicted HOMA-IR

after adjustment for age, sex, BMI, diabetes duration, triglycerides and medication use.

A two-sided p-value <0.05 would be considered statistically significant.

Results

Participant Characteristics

A total of 180 patients with T2DM were included. The mean age was 52.8 ± 9.7 years, with a mean diabetes duration of 8.1 ± 5.4 years.

The mean BMI was 28.6 ± 4.1 kg/m². Mean HbA1c was $7.8 \pm 1.3\%$, while mean fasting glucose was 154.6 ± 42.8 mg/dL.

The mean HOMA-IR was 3.42 ± 1.87 .

Table 1. Baseline Clinical and Biochemical Characteristics of the Study Population

Variable	Overall population (n=180)
Age, years	52.8 ± 9.7
Male sex, n (%)	98 (54.4)
Female sex, n (%)	82 (45.6)
Diabetes duration, years	8.1 ± 5.4
BMI, kg/m ²	28.6 ± 4.1
Systolic BP, mmHg	136.8 ± 16.2
Diastolic BP, mmHg	82.4 ± 9.5
Fasting plasma glucose, mg/dL	154.6 ± 42.8
Fasting insulin, μ U/mL	9.8 ± 5.7
HbA1c, %	7.8 ± 1.3
HOMA-IR	3.42 ± 1.87
Total cholesterol, mg/dL	198.7 ± 41.5
LDL-C, mg/dL	119.4 ± 32.7
HDL-C, mg/dL	43.6 ± 9.8
Triglycerides, mg/dL	176.8 ± 74.3
Creatinine, mg/dL	0.94 ± 0.21

Values are presented as mean $\pm$ SD unless otherwise indicated.

Autophagy-Related Markers According to Glycemic Control

In the dataset, participants with HbA1c $\geq 7\%$ demonstrated higher LC3-II/LC3-I ratio, Beclin-1, ATG5 and p62 expression than those with HbA1c $< 7\%$.

The increase in p62 alongside LC3-II was interpreted cautiously because simultaneous elevation of these markers may indicate increased autophagosome formation accompanied by incomplete degradation rather than enhanced autophagic flux.

Table 2. Autophagy-Related Markers According to Glycemic Control

Marker	HbA1c $< 7\%$ (n=72)	HbA1c $\geq 7\%$ (n=108)	p-value
LC3-II/LC3-I ratio	0.86 ± 0.24	1.18 ± 0.37	< 0.001
p62 relative expression	0.92 ± 0.28	1.31 ± 0.44	< 0.001
Beclin-1 relative expression	0.94 ± 0.25	1.22 ± 0.34	< 0.001
ATG5 relative expression	0.97 ± 0.26	1.19 ± 0.31	< 0.001
p-AMPK/AMPK ratio	1.08 ± 0.31	0.79 ± 0.25	< 0.001
p-mTOR/mTOR ratio	0.92 ± 0.27	1.17 ± 0.35	< 0.001

Correlation Between Autophagy Markers and Metabolic Parameters

In the analysis, LC3-II/LC3-I showed positive correlations with HbA1c and HOMA-IR.

p62 demonstrated the strongest positive correlation with HOMA-IR, whereas the p-AMPK/AMPK ratio showed an inverse correlation.

Table 3. Correlation of Autophagy-Related Markers With Glycemic and Insulin-Resistance Parameters

Marker	HbA1c	Fasting glucose	HOMA-IR
LC3-II/LC3-I	$r=0.48, p<0.001$	$r=0.42, p<0.001$	$r=0.51, p<0.001$
p62	$r=0.56, p<0.001$	$r=0.49, p<0.001$	$r=0.61, p<0.001$
Beclin-1	$r=0.37, p<0.001$	$r=0.34, p<0.001$	$r=0.39, p<0.001$

Marker	HbA1c	Fasting glucose	HOMA-IR
ATG5	r=0.31, p<0.001	r=0.29, p<0.001	r=0.35, p<0.001
p-AMPK/AMPK	r=-0.39, p<0.001	r=-0.34, p<0.001	r=-0.44, p<0.001
p-mTOR/mTOR	r=0.33, p<0.001	r=0.30, p<0.001	r=0.38, p<0.001

Multivariable Analysis

A multivariable regression model demonstrated that p62, LC3-II/LC3-I and BMI were independently associated with HOMA-IR after adjustment for age, sex, diabetes duration, triglycerides and antidiabetic medication.

Table 4. Multivariable Regression Analysis for HOMA-IR

Predictor	β coefficient	95% CI	p-value
LC3-II/LC3-I	0.31	0.14–0.48	<0.001
p62	0.38	0.21–0.55	<0.001
Beclin-1	0.12	-0.03–0.27	0.115
ATG5	0.09	-0.05–0.23	0.201
p-AMPK/AMPK	-0.24	-0.39 to -0.09	0.002
BMI	0.27	0.14–0.40	<0.001
Diabetes duration	0.11	0.01–0.21	0.034
Triglycerides	0.16	0.04–0.28	0.009

Discussion

The present study was designed to investigate whether autophagy-related metabolic adaptation is associated with glycemic control and insulin resistance in patients with T2DM. The principal finding in the illustrative dataset was that increased LC3-

II/LC3-I and p62 expression were associated with higher HbA1c and HOMA-IR. Alterations in Beclin-1 and ATG5 were also associated with poorer metabolic status, while the p-AMPK/AMPK ratio showed an inverse relationship with insulin resistance.

The relationship between autophagy and T2DM is biologically plausible because autophagy participates in the maintenance of cellular quality control and energy metabolism. It can remove damaged mitochondria and proteins and recycle intracellular substrates during periods of metabolic stress.³ However, chronic nutrient excess, hyperglycemia, lipid accumulation, oxidative stress and endoplasmic reticulum stress can disrupt normal autophagic regulation.²

An important interpretation of the present findings is that increased autophagy-associated markers should not automatically be interpreted as increased functional autophagy. LC3-II accumulation may reflect increased autophagosome formation, reduced lysosomal degradation, or both. Similarly, p62 accumulation may indicate insufficient degradation of autophagic cargo.⁶

The simultaneous increase in LC3-II/LC3-I and p62 observed in the poorly controlled group therefore represents a potentially interesting metabolic adaptation. Rather than describing this simply as “autophagy activation,” it may be more accurate to describe it as altered autophagy-associated signaling with evidence suggestive of incomplete autophagic processing.

This distinction is supported by recent human evidence. A comprehensive review of human studies found that autophagic alterations in obesity and T2DM are heterogeneous and may differ according to tissue, disease stage and metabolic context. Some evidence suggests increased autophagosome formation during hyperglycemia or insulin resistance, while prolonged metabolic stress may impair downstream autophagic flux.²

The present findings are also consistent with earlier human observations in circulating leukocytes. Patients with T2DM have been reported to demonstrate increased LC3-II and Beclin-1 together with markers of oxidative and endoplasmic reticulum stress.⁷ These observations suggest that circulating cells can reflect systemic metabolic stress-related changes in autophagy.

The positive relationship between p62 and HOMA-IR is particularly noteworthy. p62 participates in selective autophagy and interacts with several signaling pathways involved in metabolism and inflammation. Persistent accumulation of p62 may therefore represent impaired degradation or altered stress signaling. Nevertheless, a cross-sectional association cannot establish whether p62 accumulation contributes to insulin resistance or is a consequence of metabolic stress.

AMPK provides another important mechanistic link. AMPK is an energy-sensing kinase that responds to cellular energy status and can promote autophagy.⁵ In contrast, nutrient- and growth-factor-dependent mTOR signaling generally suppresses autophagy initiation. The inverse association between AMPK activation and HOMA-IR in the dataset therefore provides a biologically coherent relationship between energy sensing and metabolic dysfunction.

However, AMPK-mTOR signaling is highly context dependent. Diabetes is not simply a state of universally reduced AMPK activity or universally increased mTOR activity. Tissue-specific effects, nutritional status, medications, exercise, obesity and disease duration can modify these pathways. Consequently, the present study should interpret these markers as components of a broader metabolic signaling network rather than isolated determinants.

The relationship between autophagy and pancreatic β -cell function is also important. Experimental evidence indicates that basal autophagy is necessary for maintenance of β -cell mass and intracellular quality control. Dysregulated autophagy can increase vulnerability to glucolipotoxicity and endoplasmic reticulum stress.⁴

Human skeletal-muscle studies further demonstrate that autophagy may undergo metabolic adaptation rather than complete failure in T2DM. One study examining skeletal muscle in individuals with T2DM found that autophagy-related gene and protein levels were broadly preserved, while insulin-associated changes in LC3B and p62 were altered.⁸ This supports the concept that the metabolic environment may modify autophagy dynamics without necessarily eliminating autophagic machinery.

The clinical significance of these findings is potentially important. HbA1c summarizes longer-term glycemic exposure, whereas HOMA-IR provides an estimate of insulin resistance based on fasting glucose and insulin.¹⁰ If autophagy-related markers demonstrate reproducible associations with these metabolic indices, they could potentially serve as research biomarkers for identifying cellular metabolic stress phenotypes.

Nevertheless, the present cross-sectional design does not establish causality. It cannot determine whether dysregulated autophagy causes insulin resistance, whether insulin resistance causes altered autophagy, or whether both are consequences of common metabolic stressors such as obesity,

hyperglycemia, inflammation and lipid excess.

Medication use is another important consideration. Metformin, for example, can influence AMPK-related metabolic signaling and autophagy pathways.⁴ Therefore, medication exposure should be carefully recorded and incorporated into statistical models. Other glucose-lowering therapies may also indirectly influence cellular metabolism through changes in glucose concentrations, insulin exposure, weight, or lipid metabolism.

The use of PBMCs is another limitation. PBMC autophagy markers do not necessarily reproduce autophagic activity in skeletal muscle, liver, adipose tissue or pancreatic β -cells. However, PBMCs provide a relatively accessible human model that avoids invasive tissue biopsy and may be useful for exploratory biomarker studies.

Overall, the study supports a model in which chronic metabolic stress in T2DM is accompanied by altered autophagy-associated signaling. The combination of increased LC3-associated signal and p62 accumulation may indicate an adaptive but potentially incomplete response to persistent metabolic stress. Future longitudinal studies incorporating functional autophagic-flux assays and tissue-specific measurements are

required to determine whether these changes are predictive of deterioration in insulin sensitivity or glycemic control.

Strengths of the Study

1. The study evaluates several autophagy-related markers rather than relying on a single biomarker.
2. Autophagy-related measurements are analyzed alongside clinically relevant metabolic parameters.
3. HbA1c and fasting glucose provide complementary measures of glycemic status.
4. HOMA-IR provides an additional quantitative measure of insulin resistance.
5. AMPK and mTOR signaling are incorporated to provide metabolic context for autophagy-associated changes.
6. Multivariable analysis allows adjustment for important metabolic confounders.
7. The study uses PBMCs, providing a practical and minimally invasive approach for human translational research.

Limitations

First, the cross-sectional design prevents determination of temporal or causal relationships.

Second, PBMC autophagy markers may not accurately represent autophagy in insulin-sensitive tissues such as skeletal muscle, liver or adipose tissue.

Third, LC3, p62, Beclin-1 and ATG5 are static molecular measurements and cannot independently establish autophagic flux.

Fourth, HOMA-IR is an indirect estimate of insulin resistance and is influenced by fasting insulin assay characteristics and β -cell function.

Fifth, antidiabetic medications may affect metabolic signaling and autophagy-related pathways.

Sixth, residual confounding by diet, physical activity, obesity, sleep, inflammation and other metabolic factors cannot be completely excluded.

Finally, the study should ideally be validated using functional autophagic-flux assays, longitudinal follow-up, and tissue-specific or extracellular-vesicle-based biomarkers.

Conclusion

Autophagy-related metabolic adaptation represents a potentially important component of the cellular response to chronic metabolic stress in T2DM. In the illustrative analysis, altered LC3-II/LC3-I, p62, Beclin-1, ATG5, AMPK and mTOR signaling were associated with HbA1c and insulin resistance.

The concurrent elevation of LC3-associated and p62 signals should not be interpreted simply as enhanced functional autophagy; rather, it may indicate increased autophagy-associated activity together with incomplete

downstream processing. This distinction is important because static autophagy markers do not directly measure autophagic flux.

Further prospective studies incorporating functional flux assays, larger populations and tissue-specific biomarkers are warranted to determine whether autophagy-related metabolic signatures can serve as clinically useful biomarkers or therapeutic targets in T2DM.

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