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Article

Obesity as a Disease of Visceral Adipose Tissue: MMP Activation and AGE Accumulation as Key Mechanisms of Metabolic Complications

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Abstract

Obesity is increasingly recognized as a chronic molecular disease of visceral adipose tissue rather than a simple excess of body weight. Structural remodeling and biochemical damage within adipose depots — particularly extracellular matrix (ECM) degradation and oxidative protein modification — are believed to play a central role in the development of metabolic complications. This study evaluated matrix metalloproteinase (MMP) activity and protein glycooxidation in visceral and subcutaneous adipose tissue, as well as plasma in individuals with obesity. Using a fluorescence resonance energy transfer (FRET)-based assay and fluorimetric quantification of advanced glycation end-products (AGEs), we demonstrated markedly increased activity of all analyzed MMPs (MMP-1, -2, -7, -9, -11, -13) and significantly higher accumulation of selected AGE-related structures (dityrosine (DT), amyloid cross- β -structure, vesperlysine (VES), pentosidine (PEN)) in visceral adipose tissue of obese patients. These findings indicate that visceral adipose tissue forms a localized inflammatory-proteolytic microenvironment rather than a reflection of systemic circulating pathology. The coexistence of ECM degradation and glycooxidation may mechanistically promote insulin resistance and cardiometabolic risk. These findings suggest that clinical assessment of obesity may require more than anthropometric parameters and circulating biomarkers. Molecular profiling of visceral adipose tissue — directly or via future non-invasive surrogate markers — could improve patient stratification, support personalized metabolic risk prediction and optimize therapeutic decision-making.

Keywords: obesity; visceral adipose tissue; subcutaneous adipose tissue; matrix metalloproteinases; extracellular matrix remodeling; advanced glycation end-products; glycooxidation; metabolic complications; adipose tissue inflammation; tissue remodeling

Study Highlights — What is New

- This is the first human study to simultaneously quantify MMP activity and glycooxidation-derived AGE structures in paired visceral and subcutaneous adipose tissue.

- Molecular abnormalities of obesity are restricted to visceral adipose tissue; subcutaneous adipose tissue and plasma remain unaffected.
- The coexistence of ECM proteolysis and protein glycooxidation indicates a synergistic mechanism leading to adipose tissue failure.
- Circulating biomarkers do not reflect visceral adipose tissue pathology, explaining why metabolic risk cannot be reliably stratified using blood tests alone.
- Visceral adipose tissue behaves as a metabolically active inflammatory–proteolytic organ, supporting the concept of obesity as a disease of adipose tissue quality rather than adipose mass.

1. Introduction

Obesity is one of the most pressing global health challenges and is strongly associated with type 2 diabetes, dyslipidemia and cardiovascular disease [1,2]. Current scientific understanding emphasizes that obesity is not merely a consequence of caloric excess, but a progressive systemic disease driven by chronic low-grade inflammation and qualitative disturbances in adipose tissue structure [3,4]. Among adipose depots, visceral adipose tissue is considered the most clinically relevant due to its distinct endocrine profile, metabolic activity and inflammatory potential.

The expansion of visceral adipose tissue triggers hypoxia, immune cell recruitment, oxidative stress and remodeling of the ECM, ultimately promoting fibrosis [4]. A central regulator of ECM homeostasis is the family of Matrix Metalloproteinases (MMPs). Dysregulated MMP activity has been linked to adipose tissue fibrosis, endothelial dysfunction, insulin resistance and cardiometabolic risk [5–7]. Notably, excessive MMP activity can also modify adipokine signaling and increase leptin resistance, further deepening metabolic deterioration [8]. Beyond adipokine dysregulation, excessive MMP activity contributes to oxidative stress by disrupting antioxidant ECM structures and releasing ROS-generating fragments. This oxidative shift enhances the biochemical milieu in which non-enzymatic protein glycation and glycooxidation readily occur.

In parallel, metabolic stress induces non-enzymatic protein glycation and glycooxidation, leading to the accumulation of AGEs. AGEs irreversibly alter protein structure, amplify oxidative stress and activate pro-inflammatory pathways through receptors such as receptor for advanced glycation end-products (RAGE) [2]. Although both MMP activation and AGE accumulation have been implicated in metabolic disease, their coexistence at the adipose tissue level has not been comprehensively investigated.

Most available studies focus on circulating markers, which may not reliably reflect local molecular adipose tissue pathology. Therefore, this study evaluates whether visceral adipose tissue in obesity constitutes a selective inflammatory–proteolytic niche characterized by simultaneous activation of MMPs and glycooxidation-related protein damage, in contrast to subcutaneous adipose tissue and plasma. This divergence arises from the inherently higher immunometabolic activity of visceral fat, which possesses richer vascularization, denser macrophage infiltration and greater exposure to gut-derived inflammatory mediators compared with subcutaneous fat [2,4,6].

2. Materials and Methods

2.1. Metalloproteinase Activity

To assess the activity of various MMPs in subcutaneous and visceral fat, as well as plasma, we used a previously described FRET assay [9]. Before the assay, the samples were pre-incubated at 37°C with 2mM 4-aminophenylmercuric acetate (APMA). The incubation times varied depending on the MMP type (3 hours for MMP-1; 1 hour for MMP-2 and MMP-7; 2 hours for MMP-9; 40 minutes for MMP-13). Only MMP-11 did not require pre-incubation, as it is already in its active form. After pre-incubation, the MMP-containing sample was mixed with the Tris-HCl/NaCl/CaCl₂ (TNC) assay buffer, and 3 μM MMP substrate (MCA-Pro-Leu-Gly~Leu-Dpa(Dnp)-Ala-Arg-NH₂, containing the

FRET peptide was added. The substrate was obtained from Sigma-Aldrich. Typically, the FRET peptide contains a fluorophore on one side of the peptide sequence and a quencher on the other. When the protein is intact, the quencher suppresses the emission peak of the fluorophore and absorbs its energy in a distance-dependent manner. However, when active MMPs are present, the peptide is cleaved into two separate fragments, allowing the fluorescence from the fluorophore to be detected. The mixture was incubated at 37°C for 1h, after which the stop solution was added, and fluorescence was measured. The data were presented as arbitrary fluorescence units (AFU) per 1 milligram of protein. Figure 1 represents a simplified version of the process.

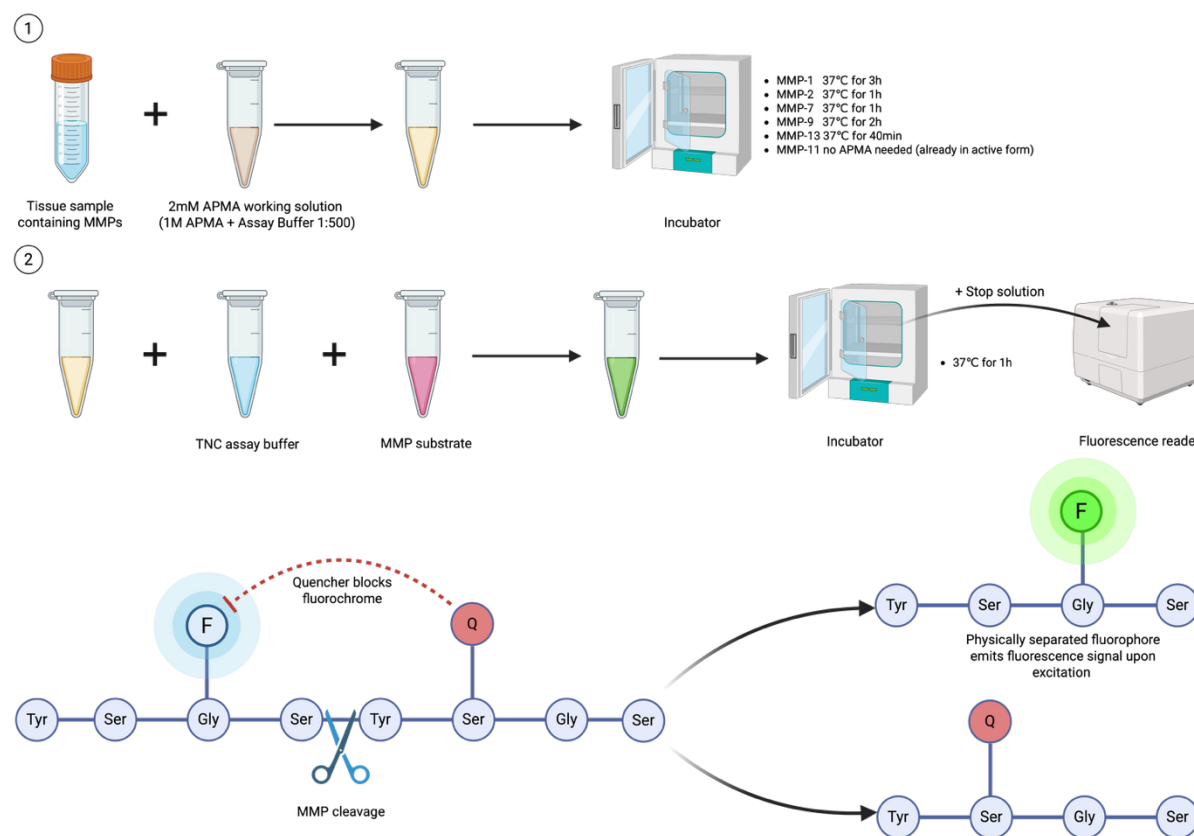


Figure 1. Schematic representation of the FRET-assay used to measure MMPs activity. Created with BioRender.com. APMA – 4-Aminophenylmercuric acetate; MMPs – metalloproteinases; TNC - Tris-HCl/NaCl/CaCl₂.

2.1. Advanced Glycation Products

Total AGE and specific AGEs such as VES, PEN and amyloid cross- β -structure were assessed using fluorimetric analysis. Additionally, we measured protein glycooxidation product - DT. Fluorescence measurements were performed using an Infinite M200 PRO multi-mode plate reader (Tecan Group Ltd., Männedorf, Switzerland). The samples were diluted in 0.02 MPBS (pH 7.4; 1:5, v/v) before analysis. The excitation/emission wavelength was set at 350/440nm for total AGE, 350/405nm for VES, 335/385nm for PEN, 365/480nm for DT and 435/485nm for amyloid cross- β -structure.

3. Results

3.1. Characteristics of the Obesity Group

The obesity group consisted of 40 patients with severe obesity qualified for bariatric surgery according to the criteria specified in the Individual Research Project, including BMI > 35 kg/m² and the absence of active malignancy, acute inflammatory diseases, autoimmune disorders, chronic infectious diseases and alcohol or nicotine dependence.

There were 28 women and 12 men. The median age of the patients was 43 years (interquartile range [IQR]: 35–50 years), with a range from 20 to 73 years, and a mean age of 42.6 ± 12.1 years.

Anthropometric data confirmed advanced obesity. The median body weight was 113 kg (IQR: 97–136.5 kg, range: 82–185 kg) and the median BMI was 39.24 kg/m^2 (IQR: $36.19\text{--}44.41 \text{ kg/m}^2$, range: $32.37\text{--}51.79 \text{ kg/m}^2$).

Median height was approximately 1.7 m.

Laboratory data were consistent with a chronic low-grade inflammatory state: the median CRP concentration was 13.6 mg/L (IQR: 7.6–26.0 mg/L, range: 3.7–85.9 mg/L), the median fibrinogen level was 358 mg/dL (IQR: 323–391 mg/dL, range: 258–484 mg/dL) and the median white blood cell count was $11.19 \times 10^3/\mu\text{L}$ (IQR: $9.9\text{--}12.47 \times 10^3/\mu\text{L}$, range: $5.73\text{--}17.92 \times 10^3/\mu\text{L}$).

In total, 15 patients met the criteria for metabolic syndrome. Surgical procedures included 29 sleeve gastrectomies (one combined with crural repair to prevent gastroesophageal reflux symptoms), 9 gastric bypass procedures (one combined with hiatal hernia repair) and 2 SADI procedures. Overall, the study cohort represents a typical population of patients with severe obesity referred for bariatric surgery, with a high burden of metabolic complications and chronic inflammation, but without comorbidities that would exclude participation in the study.

A detailed summary of the anthropometric and biochemical characteristics of the obesity group is presented in Table 1.

Table 1. Baseline anthropometric and biochemical characteristics of the obesity group. Values are presented as minimum, median with 25th–75th percentiles and maximum values for the study population. Data include anthropometric, hematological and biochemical parameters measured prior to bariatric surgery.

Parameter	Minimum	25th percentile	Median	75th percentile	Maximum
Height (m)	1.53	1.64	1.78	1.67	1.97
Body weight (kg)	82	97	113	136.5	185
BMI (kg/m^2)	32.37	36.19	39.24	44.41	51.79
CRP (mg/L)	3.7	7.6	13.6	26	85.9
Urea (mg/dL)	14.98	21.4	27.82	35.85	66.34
Creatinine (mg/dL)	0.52	0.625	0.74	0.945	1.24
Amylase (IU/L)	23	34	39	62	79
Total bilirubin (mg/dL)	0.32	0.56	0.74	0.945	1.24
ALT (IU/L)	14	22	28.5	50.75	200
AST (IU/L)	16	23.25	29	45	207
Potassium (mmol/L)	3.7	4.125	4.3	4.5	5.2
Sodium (mmol/L)	136	137.3	139	140.8	146
WBC ($\times 10^3 \mu\text{L}$)	5.73	9.9	11.19	12.47	17.92
RBC ($\times 10^6 \mu\text{L}$)	3.52	4.03	4.43	4.72	5.55
Hemoglobin (g/dL)	10.4	12.3	13.1	13.9	14.9
Hematocrit (%)	31.6	36.7	39.2	42.3	46.1
MCV (fL)	82	85.3	88.4	91.1	93.4
MCH (pg)	25.3	28.7	29.4	30.2	32.6
MCHC (g/dl)	30	32.4	33.4	34.2	35.9
Platelets ($\times 10^3 \mu\text{L}$)	123	212	243	280	353
Fibrinogen (mg/dL)	258	323	358	391	484
INR	0.93	1.00	1.05	1.17	1.41

3.2. Characteristics of the Control Group.

The control group consisted of 21 patients qualified for elective surgical procedures in accordance with the inclusion and exclusion criteria defined in the Individual Research Project, including the absence of obesity, metabolic disorders, autoimmune diseases, active malignancy, acute

or chronic inflammatory diseases and alcohol or nicotine dependence. The group included 13 women and 8 men. The median age was 50 years (interquartile range [IQR]: 39–66 years), with a range of 25 to 78 years.

The median BMI in the control group remained within the reference range for the majority of individuals, although a few patients presented BMI values above 25 kg/m². This deviation was accepted due to the considerable difficulty in obtaining a sufficiently large number of eligible healthy volunteers. Additional bioethics committee approval was obtained to increase recruitment and ensure adequate statistical power of the study.

All laboratory inflammatory markers were within reference ranges, which was consistent with the inclusion criteria and confirmed the absence of systemic inflammation. Surgical indications included 17 hernia repair procedures and 4 laparoscopic cholecystectomies, with no history of metabolic or bariatric surgery in any participant.

3.3. Ethical Approval and Informed Consent

The study was conducted in accordance with the Declaration of Helsinki and approved by the Bioethics Committee of the Medical University of Białystok (resolution No. APK.002.98.2023, issued on 16 February 2023). An additional approval was obtained by resolution No. R-I-002/475/2019, issued on 19 September 2024, which authorized the Humana Medica Omeda center as an additional site for biological sample collection and permitted the continuation of the medical experiment at this location. Informed consent was obtained from all participants prior to inclusion in the study. Each patient signed the Patient Information Form describing the study objectives, procedures and potential risks, as well as the Consent Form for participation in scientific research and Annex No. 1 and Annex No. 2 to the Personal Data Protection Rules for Research at the Medical University of Białystok.

3.4. Metalloproteinase Activity

MMPs are zinc-dependent proteases responsible for cleaving and modifying ECM components, including collagen, elastin, and gelatin. They have an essential role in numerous physiological processes, such as cell-cycle regulation, signal transduction, cell differentiation and ECM turnover [10]. These functions are important for normal growth and morphogenesis. Indeed, an increased MMPs activity was observed during embryogenesis, angiogenesis, wound repair and bone development [11]. Conversely dysregulated MMPs activity can be associated with a variety of pathological conditions, including inflammation, fibrosis, autoimmune diseases, diabetes mellitus, and cancer progression and metastases [11].

In our study we found that visceral fat MMP activity in obese patients was significantly increased compared to the control group with the following percentage changes: MMP-1 (MD +54.74%; $p < 0.0001$), MMP-2 (MD +54.49%; $p < 0.0001$), MMP-7 (MD +56.59%; $p < 0.0001$), MMP-9 (MD +53.07%; $p < 0.0001$), MMP-11 (MD +58.21%; $p = 0.0001$), MMP-13 (MD +57.56%; $p < 0.0001$) (Figure 2). No significant difference in MMPs activity were observed in plasma and subcutaneous fat for any of the assessed MMPs.

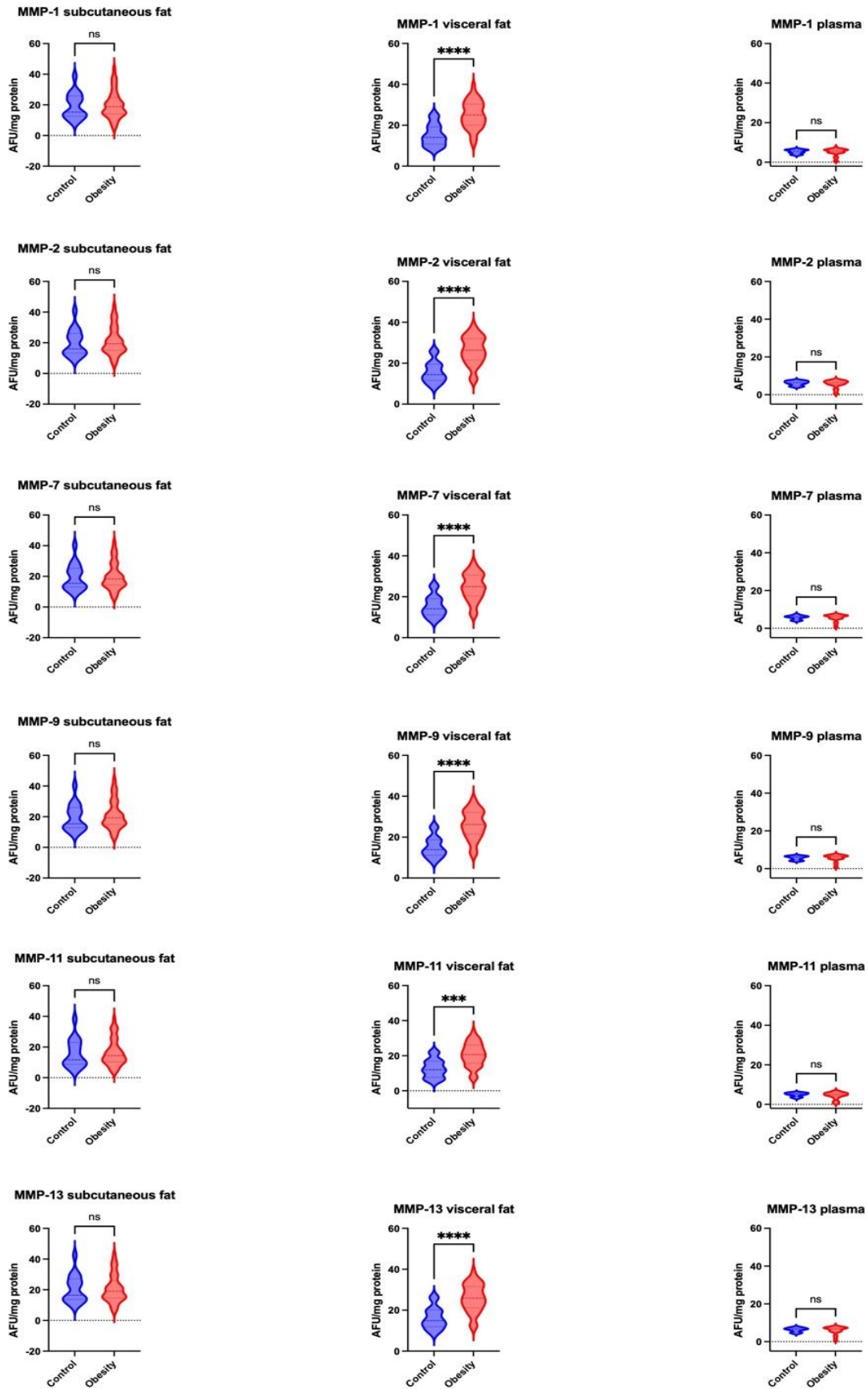


Figure 2. Comparison of metalloproteinase activity in different tissues in obese and healthy individuals. MMP – metalloproteinase (-1, -2, -7, -9, -11, -13); ns – not significant; *** p < 0.001; **** p < 0.0001. Data are presented as mean \pm SEM. Statistical significance was calculated using ANOVA followed by post hoc test.

3.5. Advanced Glycation Products

Protein glycation is a non-enzymatic process in which a free amino group reacts with the carbonyl group, forming an unstable Schiff base. This intermediate then undergoes rearrangement into a more stable Amadori product (AP). Ultimately, APs can further promote protein degradation by generating AGEs with a prolonged half-life [12,13]. These changes alter protein structure and function, making it resistant to modifications and breakdown. This leads to the accumulation of damaged proteins, resulting in inflammation and various pathological conditions, including diabetes mellitus, cardiovascular diseases, and neurodegenerative diseases [14].

VES and PEN are the final glycation products. Amyloid cross- β -structure is a peptide that is especially prone to glycation and forms deposits present in Alzheimer's disease [12]. DT is a byproduct of glycooxidation that arises when the reactive oxygen species (ROS) interact with glycated proteins, resulting in more complex alterations [14].

3.5.1. Dityrosine

We observed a significant increase in visceral fat levels in DT (MD +72.47%; $p < 0.05$) among obese patients vs controls. There were no significant differences in subcutaneous fat and plasma levels between the two groups (Figure 3).

3.5.2. Amyloid Cross- β -Structure

Levels of amyloid cross- β -structure were significantly greater in visceral fat of obese patients compared to controls (MD +61.85%; $p < 0.001$). Additionally, the obese group had a higher plasma concentration than the control group (MD +67.99%; $p < 0.01$). There was no significant change in subcutaneous fat concentration between the groups (Figure 3).

3.5.3. Vesperlysine

We observed a significantly higher VES content in visceral fat in obese individuals compared to controls (MD +69.76%; $p < 0.01$). There was no significant difference in VES content in subcutaneous fat or plasma (Figure 3).

3.5.4. Pentosidine

PEN levels were significantly higher in the obese group compared to controls (MD +72.77%; $p < 0.05$). There was no difference between the groups in subcutaneous fat or plasma (Figure 3).

3.5.5. Total AGE

The total AGE content did not significantly differ across all the groups and tissues (Figure 3)

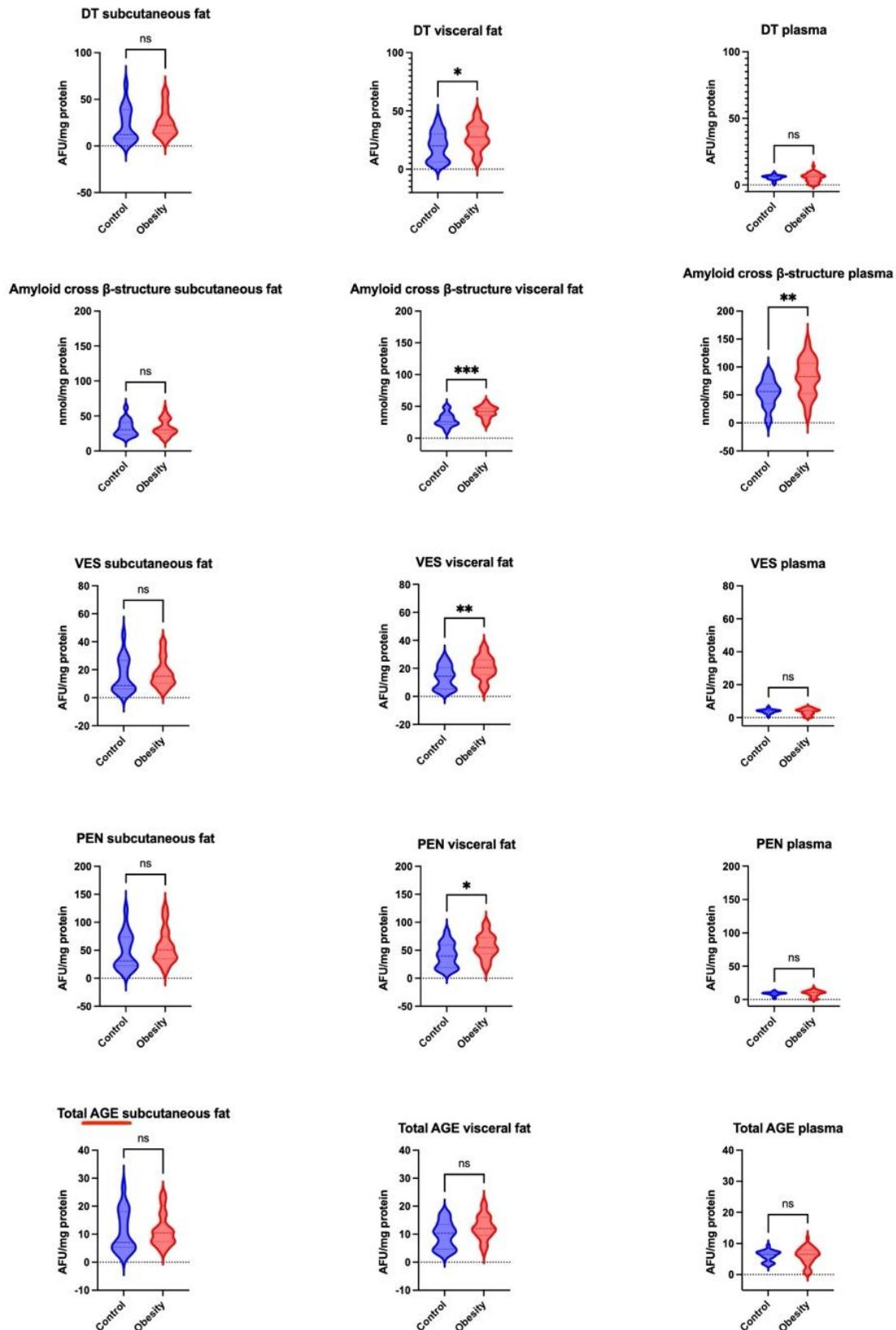


Figure 3. Concentration of advanced glycation products in different tissues in obese and healthy individuals. AGE – advanced glycation end-product; DT – dityrosine; PEN – pentosidine; VES – vesperlysine; ns – not significant; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. Data are presented as mean \pm SEM. Statistical significance was calculated using ANOVA followed by post hoc test.

4. Discussion

This study provides new insight into the pathophysiology of obesity by showing that proteolytic and glycooxidative changes occur selectively within visceral adipose tissue. The consistent upregulation of activity across all analyzed MMP isoforms in visceral adipose tissue — particularly MMP-1, MMP-2, MMP-7 and MMP-9 — coupled with the unchanged activity in subcutaneous adipose tissue and plasma, indicates that ECM breakdown is not a systemic feature of obesity but rather a highly localized hallmark of visceral adipose tissue dysfunction. Similarly, pronounced elevations in DT, amyloid cross- β -structure, VES and PEN were restricted to visceral adipose tissue, while total AGE concentrations remained unchanged, underscoring a targeted and structured molecular alteration rather than a global rise in glycooxidation

Local Molecular Pathology in Visceral Fat as the Driver of Metabolic Deterioration

Although obesity is commonly characterized as a systemic inflammatory condition, our findings highlight that circulating markers overlook critical tissue-level pathology. This is consistent with studies emphasizing that metabolic risk is attributable not to total adipose mass but to qualitative dysfunction of visceral adipose tissue [1,4]. Expanding visceral adipose tissue undergoes hypoxia-induced oxidative stress and immune infiltration, initiating ECM remodeling and fibrosis that impair adipocyte expandability [2,5]. The strong activation of MMPs observed in our data indicates continuous ECM breakdown, which has been implicated in adipose tissue instability and enhanced recruitment of inflammatory cells [5,6]. Notably, proteolytic cleavage of key adipokine receptors — such as cleavage of the leptin receptor by MMP-2 — has been proposed as a mechanism exacerbating metabolic deterioration [8].

Synergy Between ECM Proteolysis and Glycooxidation as a Mechanistic Link

The observed parallel between elevated MMP activity and increased AGE accumulation suggests a synergistic mechanism rather than two independent processes. ECM degradation exposes proteins susceptible to oxidative modifications, while AGE-mediated crosslinking subsequently stiffens the ECM, perpetuating inflammation and fibrosis [2]. This cycle ultimately impairs lipid buffering capacity and promotes a maladaptive shift toward increased lipolysis, elevated free fatty acid flux and hepatic gluconeogenesis — key drivers of insulin resistance and atherogenic dyslipidemia [15]. These results therefore support a paradigm in which visceral adipose tissue dysfunction precedes and drives systemic metabolic disease, rather than appearing as its consequence.

Why Circulating Biomarkers Fail to Stratify Metabolic Risk

An important implication of these findings is the mismatch between molecular pathology in adipose tissue and detectable systemic markers. Despite pronounced proteolytic and glycooxidative alterations in visceral adipose tissue, plasma MMP and AGE markers remained largely unchanged. This explains why conventional laboratory tests poorly distinguish metabolically healthy obesity from metabolically unhealthy obesity and why patients with similar BMI values often present radically different metabolic risks. A pathologic visceral depot can therefore remain biochemically invisible to routine diagnostics.

Translational Implications

These insights have direct therapeutic relevance. Bariatric surgery and incretin-based pharmacotherapy have been shown to reduce systemic inflammation, oxidative stress and normalize circulating MMP levels [16–19]. Interventions that improve ECM homeostasis and reduce fibrotic signaling are associated with improved insulin sensitivity, metabolic disorders and cardiometabolic outcomes [18,20,21]. However, it remains unknown to what extent tissue-level glycooxidation and fibrosis are reversible, and whether a durable “metabolic scar” persists despite weight loss. Future

clinical studies will need to integrate metabolic outcomes with tissue-specific molecular profiling to determine whether normalization of visceral adipose tissue biology is a prerequisite for full metabolic recovery.

Strengths, Limitations and Perspectives

A major strength of this study is the direct molecular assessment of human adipose tissue depots from the same individuals, in contrast to exclusive reliance on circulating biomarkers. This design allowed us to clearly separate systemic from local pathology. Limitations include the cross-sectional design, which restricts inference about temporal causality, and the absence of additional ECM-associated markers (e.g., tissue inhibitors of metalloproteinases (TIMPs), collagen subtypes, integrin signaling).

5. Conclusions

The present study demonstrates that visceral adipose tissue in obesity constitutes a selective inflammatory–proteolytic microenvironment characterized by concurrent activation of matrix metalloproteinases and glycooxidation-related protein damage. This pattern was not observed in subcutaneous adipose tissue nor in plasma, indicating that circulating biomarkers may substantially underestimate local molecular injury within visceral fat. These findings highlight the role of visceral adipose tissue as a key driver of metabolic deterioration rather than a passive energy reservoir. By identifying the tight link between ECM proteolysis and protein glycooxidation, the study provides mechanistic insight into adipose tissue dysfunction and offers a potential molecular framework for future therapeutic targeting. Further longitudinal and interventional studies are likely necessary to determine whether modulation of MMP activity or attenuation of AGE accumulation within visceral fat can translate into improved metabolic outcomes.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Bioethics Committee of the Medical University of Białystok (resolution No. APK.002.98.2023 of 16 February 2023) and by resolution No. R-I-002/475/2019 of 19 September 2024, which authorized the Humana Medica Omeda center as an additional site for biological sample collection and permitted the continuation of the medical experiment.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study. Each participant signed the Patient Information Form describing the study procedures and risks, as well as the Consent Form for participation in scientific research and Annex No. 1 and Annex No. 2 to the Personal Data Protection Rules for Research at the Medical University of Białystok.

Data Availability Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request. Data are not publicly available due to personal data protection regulations.

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Abbreviations

AGE – advanced glycation end-product
 ALT – Alanine aminotransferase
 AP – Amadori product
 AST – Aspartate aminotransferase
 APMA – 4-aminophenylmercuric acetate
 BMI – body mass index
 CRP – C-reactive protein
 DT – dityrosine
 ECM – extracellular matrix
 FRET – fluorescence resonance energy transfer
 INR – International normalized ratio
 MCH – Mean corpuscular hemoglobin
 MCHC – Mean corpuscular hemoglobin concentration
 MCV – Mean corpuscular volume
 MMP – matrix metalloproteinase
 PEN – pentosidine
 RAGE – receptor for advanced glycation end-products
 RBC – Red blood cells
 ROS – reactive oxygen species
 TIMP – tissue inhibitor of metalloproteinases
 WBC – White blood cells
 VES – vesperlysine

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