

# Oxidative Stress And Metabolic Dysregulation In Type 2 Diabetes: An Adiposity-Linked Shift In Plasma Redox Balance

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**ABSTRACT :** Oxidative stress is regarded as a central mechanism in the pathogenesis of type 2 diabetes mellitus (T2DM), yet its relationship with routine metabolic indices remains incompletely characterised in Vietnamese patients. This cross-sectional study determined plasma total antioxidant status (TAS) and malondialdehyde (MDA), an end-product of lipid peroxidation, in 140 outpatients with T2DM aged 40–79 years managed at the Thai Nguyen Medical Centre between November 2024 and April 2025, and examined their associations with body mass index (BMI), waist circumference and fasting plasma glucose. TAS was measured by the Randox ABTS® assay and MDA by thiobarbituric acid spectrophotometry; associations were assessed by sex-stratified Spearman rank correlation. Overweight and obesity predominated (56.43%). Mean plasma TAS was  $1.58 \pm 0.19$  mmol/L, significantly higher in men ( $1.62 \pm 0.21$  mmol/L) than in women ( $1.54 \pm 0.15$  mmol/L;  $p = 0.011$ ), whereas mean MDA was  $2.24 \pm 0.51$  nmol/mL and did not differ between the sexes ( $p = 0.488$ ). TAS correlated weakly and inversely with BMI in both men ( $\rho = -0.305$ ;  $p = 0.008$ ) and women ( $\rho = -0.338$ ;  $p = 0.003$ ), whereas MDA showed a moderate positive correlation with BMI in men ( $\rho = 0.434$ ;  $p < 0.001$ ) and women ( $\rho = 0.515$ ;  $p < 0.001$ ); neither marker correlated significantly with fasting plasma glucose or waist circumference. The reciprocal behaviour of the two markers indicates a coordinated displacement of redox equilibrium coupled to adiposity rather than to prevailing glycaemia, suggesting that weight reduction may be the most accessible means of lowering oxidative burden in pharmacologically treated T2DM.

**Keywords:** Type 2 Diabetes Mellitus; Oxidative Stress; Malondialdehyde; Total Antioxidant Status; Adiposity; Sex Differences.

## 1. INTRODUCTION

Type 2 diabetes mellitus (T2DM) has become one of the defining non-communicable disease burdens of the present century. The International Diabetes Federation estimates that 589 million adults aged 20–79 years — 11.1% of the world's population in this age group — were living with diabetes in 2024, that this figure will rise to 853 million by 2050, and that some 95% of the projected increase will occur in low- and middle-income countries [1]. Vietnam sits squarely within this trajectory: rapid urbanisation, nutritional transition and a rising prevalence of overweight and obesity have been accompanied by a steep increase in the number of adults with diabetes, together with a large

undiagnosed fraction. T2DM is characterised by sustained elevation of plasma glucose that leads to vascular injury and to cardiovascular, neurological and renal complications, but the disorder is not confined to glucose; it is a disturbance of intermediary metabolism as a whole, in which adiposity, dyslipidaemia and insulin resistance are as central as hyperglycaemia itself.

Among the mechanisms proposed to link these components, oxidative stress has attracted particular attention. Oxidative stress arises when the generation of reactive oxygen species (ROS) exceeds the neutralising capacity of the antioxidant defence system [2–4]. Brownlee's unifying hypothesis holds that

mitochondrial overproduction of superoxide is the single upstream event that simultaneously activates the polyol, hexosamine, protein kinase C and advanced glycation end-product pathways responsible for diabetic tissue injury [5], while Ceriello and Motz proposed oxidative stress as the "common soil" from which insulin resistance,  $\beta$ -cell dysfunction and endothelial injury jointly arise [6]. Adipose tissue is a key source of this oxidant load: as fat mass expands, increased non-esterified fatty acid flux activates NADPH oxidase while the expression of antioxidant enzymes is suppressed, and the resulting local redox shift drives the dysregulated adipocytokine secretion that characterises the metabolic syndrome [7]. ROS in turn interfere with proximal insulin signalling through stress-activated kinases that phosphorylate insulin receptor substrate-1 on serine residues, reducing GLUT4-mediated glucose uptake [8]. On this view, redox imbalance is not merely a downstream consequence of hyperglycaemia but an integral component of the metabolic disturbance itself.

Two complementary laboratory indices are commonly used to capture this imbalance. Malondialdehyde (MDA), the end-product of lipid peroxidation [9], reflects the extent of oxidative damage already sustained, whereas total antioxidant status (TAS) represents the aggregate protective capacity of the plasma antioxidant system. Evidence accumulated over the past five years has consolidated the direction of change in T2DM. A meta-analysis of 22 case–control studies comprising 1,667 patients and 1,186 healthy controls found MDA and nitric oxide

significantly higher, and glutathione and TAS significantly lower, in patients with T2DM [10]; a systematic review of studies published between 2013 and 2023 identified 25 candidate markers and confirmed MDA as the most widely used [11]. More recent work has begun to disentangle the contributions of diabetes and of adiposity. In a Jordanian cross-sectional study of 406 adults, serum MDA was highest in patients with T2DM ( $0.230 \pm 0.05 \mu\text{mol/L}$ ), intermediate in obese non-diabetic individuals ( $0.207 \pm 0.06 \mu\text{mol/L}$ ) and lowest in non-obese healthy controls ( $0.135 \pm 0.04 \mu\text{mol/L}$ ) [12]. Cecerska-Heryć et al. reported that BMI, treatment modality and the presence of complications each modified antioxidant enzyme activity and inflammatory markers in patients with diabetes [13], and El Frakchi et al., studying 254 Moroccan outpatients with T2DM, found dietary total antioxidant capacity to be inversely associated with BMI, waist circumference and fat mass percentage independently of confounders [14].

Several gaps nevertheless remain. First, most published work contrasts patients with healthy controls, whereas the gradient of redox status across metabolic indices within a diabetic population - the situation the clinician actually faces is far less well described. Second, oxidant and antioxidant markers are usually reported singly, so that the reciprocity between damage and defence is rarely demonstrated in the same subjects. Third, sex-stratified analyses are scarce, despite consistent evidence of sex differences in redox biology [15] and of an adverse redox shift in post-menopausal women with diabetes attributable to hypo-oestrogenism [16,17]. Fourth, and most directly relevant here, no Vietnamese data on paired plasma TAS and MDA in patients with T2DM have been published, so the applicability of these international findings to the Vietnamese population is unknown.

The present study was therefore undertaken to determine and compare plasma TAS and MDA concentrations in male and female patients with T2DM, and to evaluate the correlations of these two indices with BMI, waist circumference and fasting plasma glucose, in order to clarify the role of oxidative stress in the metabolic disturbances of type 2 diabetes.

## 2. SUBJECTS AND METHODS

### 2.1. Study design

A cross-sectional descriptive study with an analytical component was conducted. Plasma redox markers, anthropometric measurements and fasting plasma glucose were obtained from each participant on a single occasion, and the associations among these variables were then examined. No participant was followed over time and no intervention was applied.

### 2.2. Setting and study period

The study was carried out at two sites. Participants were recruited, interviewed and measured, and venous blood was drawn, at the Thai Nguyen Medical Centre, Thai Nguyen Province. All biochemical determinations were performed at the Department of Biochemistry and Nutritional Metabolism,

National Institute of Nutrition, Hanoi. Recruitment and data collection ran from November 2024 to April 2025.

### 2.3. Study population

Inclusion criteria: patients with T2DM without established complications, receiving outpatient treatment at the Thai Nguyen Medical Centre, aged 40–79 years, and treated with insulin or metformin. T2DM was diagnosed according to the American Diabetes Association 2024 criteria (fasting plasma glucose  $\geq 7 \text{ mmol/L}$ , or HbA1c  $\geq 6.5\%$ , or random plasma glucose  $\geq 11.1 \text{ mmol/L}$ , or current use of glucose-lowering medication).

Exclusion criteria: patients with heart failure, renal failure or malignancy; patients with skeletal deformities such as kyphoscoliosis or congenital malformations; and patients who were mute, deaf, confused, or had a psychiatric disorder.

### 2.4. Sample size and sampling

The sample size was calculated using the formula for a cross-sectional descriptive study with a relative error:

$$n = Z^2_{1-\alpha/2} \times \sigma^2 / d^2$$

where  $n$  is the minimum required sample size;  $Z_{1-\alpha/2}$  is the confidence coefficient ( $Z = 1.96$  at the 95% confidence level,  $\alpha = 0.05$ );  $\sigma$  is the standard deviation of MDA or TAS concentration in adults with T2DM based on previous studies ( $\sigma = 0.92$  for MDA [18] and  $\sigma = 0.86$  for TAS [19]); and  $d$  is the absolute error relative to  $\sigma$  ( $d = 0.16$  for MDA and  $d = 0.15$  for TAS). Substituting these values yielded minimum sample sizes of 128 and 127, respectively. In practice, 140 eligible subjects were recruited.

Convenient sampling was applied: all eligible patients presenting at the Thai Nguyen Medical Centre during the data-collection period were enrolled.

### 2.5. Study variables and data-collection techniques

Anthropometric measurements (body weight, height and waist circumference) were obtained using calibrated scales and measuring tapes.

Nutritional status was assessed by body mass index (BMI), classified according to the World Health Organization criteria for Asian populations: underweight, BMI  $< 18.5 \text{ kg/m}^2$ ; normal, BMI  $18.5\text{--}22.9 \text{ kg/m}^2$ ; overweight, BMI  $23\text{--}24.9 \text{ kg/m}^2$ ; obesity class I, BMI  $25\text{--}29.9 \text{ kg/m}^2$ ; obesity class II, BMI  $\geq 30 \text{ kg/m}^2$ .

Blood sampling: venous blood was collected in the morning after an overnight fast, using heparin as anticoagulant. Samples were centrifuged and the plasma was stored at  $-20^\circ\text{C}$  until analysis. Fasting plasma glucose (mmol/L) was measured on a Beckman Coulter AU480 automated biochemistry analyser using a colorimetric method.

Plasma TAS was measured on the Beckman Coulter AU480 analyser using the Randox TAS kit (catalogue no. NX2332). The assay is based on the photometric detection of the ABTS<sup>®</sup> radical cation (2,2'-azino-di-[3-ethylbenzthiazoline sulphonate]) formed when ABTS<sup>®</sup> is oxidised by metmyoglobin and hydrogen peroxide. Antioxidants present in the sample suppress the formation of the ABTS<sup>®</sup> cation, producing a reduction in the intensity of the blue-green colour

that is proportional to the total antioxidant capacity of the sample. The absorbance was read at 600 nm and results were expressed in mmol/L; the manufacturer's reference interval for normal human plasma is 0.21–2.94 mmol/L.

Plasma MDA was quantified on a Shimadzu UV-Vis spectrophotometer by molecular absorption. Under acidic conditions and at elevated temperature, MDA reacts with thiobarbituric acid (TBA) to form a pink MDA–TBA adduct with maximum absorbance at 532 nm; absorbance is directly proportional to the MDA concentration in the sample. Results were expressed in nmol/mL; the reference interval for healthy adults is 1.0–3.0 nmol/mL, which may vary with the population and analytical method used [20].

### 2.6. Data processing and analysis

Data were cleaned, processed and analysed using SPSS version 26.0. Quantitative variables are presented as mean  $\pm$  standard deviation (SD). Differences between pairs of means were

assessed with the Student t-test or the Mann–Whitney U test as appropriate, and differences between proportions with the chi-square test. Spearman rank correlation was used to examine associations between variables. A  $p$  value  $< 0.05$  was considered statistically significant.

### 2.7. Research ethics

The study was approved by the Ethics Committee of the National Institute of Nutrition (approval no. 546/QLKH-VDD, dated 18 June 2024) and was conducted in collaboration with the University of Medicine and Pharmacy, Thai Nguyen University, and the Thai Nguyen Medical Centre. All participants were informed of the purpose, content and benefits of the study and were free to withdraw at any time.

## 3. RESULTS

**Table 1.** Anthropometric characteristics and nutritional status of the study population

| Characteristic                          | Total (n = 140)   | Male (n = 69)     | Female (n = 71)   |
|-----------------------------------------|-------------------|-------------------|-------------------|
| Body weight (kg), mean $\pm$ SD         | 59.01 $\pm$ 8.05  | 62.20 $\pm$ 6.81  | 55.90 $\pm$ 7.99  |
| Height (cm), mean $\pm$ SD              | 157.74 $\pm$ 7.11 | 162.58 $\pm$ 5.34 | 153.04 $\pm$ 5.21 |
| Waist circumference (cm), mean $\pm$ SD | 86.43 $\pm$ 8.20  | 88.47 $\pm$ 6.21  | 84.45 $\pm$ 9.38  |
| <b>Nutritional status, n (%)</b>        |                   |                   |                   |
| Underweight (BMI $< 18.5$ )             | 1 (0.71)          | 1 (1.45)          | 0 (0)             |
| Normal (BMI 18.5–22.9)                  | 60 (42.86)        | 27 (39.13)        | 33 (46.48)        |
| Overweight/obese (BMI $\geq 23$ )       | 79 (56.43)        | 41 (59.42)        | 38 (53.52)        |

SD: standard deviation; BMI: body mass index ( $\text{kg/m}^2$ ).

Within the study population, men had higher mean body weight, height and waist circumference than women. Overweight and

obesity predominated (56.43% of the whole sample) and were more frequent in men (59.42%) than in women (53.52%).

**Table 2.** Mean plasma TAS, MDA and fasting glucose concentrations in patients with type 2 diabetes mellitus

| Index                    | Group           | Mean $\pm$ SD   | $p$   |
|--------------------------|-----------------|-----------------|-------|
| TAS (mmol/L)             | Total (n = 140) | 1.58 $\pm$ 0.19 |       |
|                          | Male (n = 69)   | 1.62 $\pm$ 0.21 | 0.011 |
|                          | Female (n = 71) | 1.54 $\pm$ 0.15 |       |
| MDA (nmol/mL)            | Total (n = 140) | 2.24 $\pm$ 0.51 |       |
|                          | Male (n = 69)   | 2.27 $\pm$ 0.54 | 0.488 |
|                          | Female (n = 71) | 2.21 $\pm$ 0.48 |       |
| Fasting glucose (mmol/L) | Total (n = 140) | 7.50 $\pm$ 2.40 |       |

TAS: total antioxidant status; MDA: malondialdehyde.  $p$  values refer to the comparison between men and women.

Mean plasma TAS was significantly higher in men ( $1.62 \pm 0.21$  mmol/L) than in women ( $1.54 \pm 0.15$  mmol/L;  $p = 0.011$ ). No statistically significant difference in mean MDA concentration

was observed between the two sexes ( $2.27 \pm 0.54$  vs  $2.21 \pm 0.48$  nmol/mL;  $p = 0.488$ ).

**Table 3.** Spearman correlations of plasma TAS and MDA with fasting plasma glucose, BMI and waist circumference, by sex

| Index |        | Males  |         |        | Females |         |       |
|-------|--------|--------|---------|--------|---------|---------|-------|
|       |        | FPG    | BMI     | WC     | FPG     | BMI     | WC    |
| TAS   | $\rho$ | 0.170  | -0.305  | 0.028  | -0.050  | -0.338  | 0.190 |
|       | $p$    | 0.147  | 0.008   | 0.812  | 0.676   | 0.003   | 0.113 |
| MDA   | $\rho$ | -0.103 | 0.434   | -0.015 | -0.023  | 0.515   | 0.202 |
|       | $p$    | 0.385  | < 0.001 | 0.900  | 0.850   | < 0.001 | 0.086 |

FPG: fasting plasma glucose; BMI: body mass index; WC: waist circumference;  $\rho$ : Spearman rank correlation coefficient.

Table 3 shows that in both sexes, TAS was weakly and inversely correlated with BMI, with correlation coefficients of  $\rho = -0.305$  ( $p = 0.008$ ) in men and  $\rho = -0.338$  ( $p = 0.003$ ) in women. In neither sex was there a significant correlation between TAS and fasting plasma glucose or waist

circumference. MDA was significantly and positively correlated with BMI in both sexes: the correlation was moderate in men ( $\rho = 0.434$ ;  $p < 0.001$ ) and in women ( $\rho = 0.515$ ;  $p < 0.001$ ). No statistically significant correlation was found between MDA and fasting plasma glucose or waist circumference.

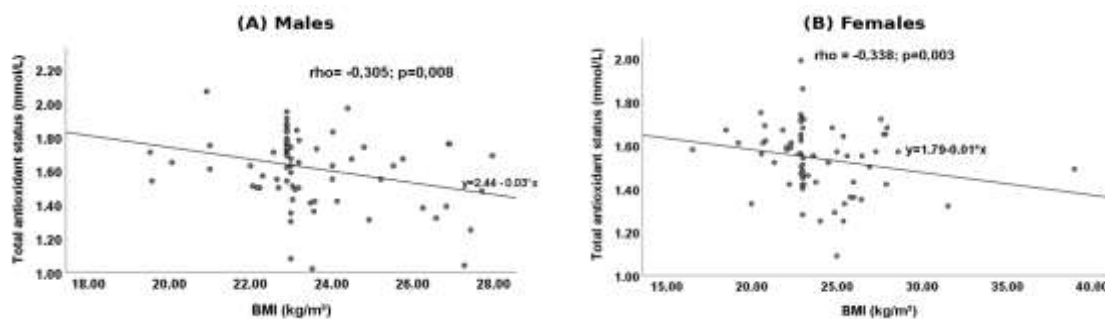


**Figure 1.** Scatter plots of the Spearman correlation between plasma TAS and BMI in patients with type 2 diabetes mellitus.

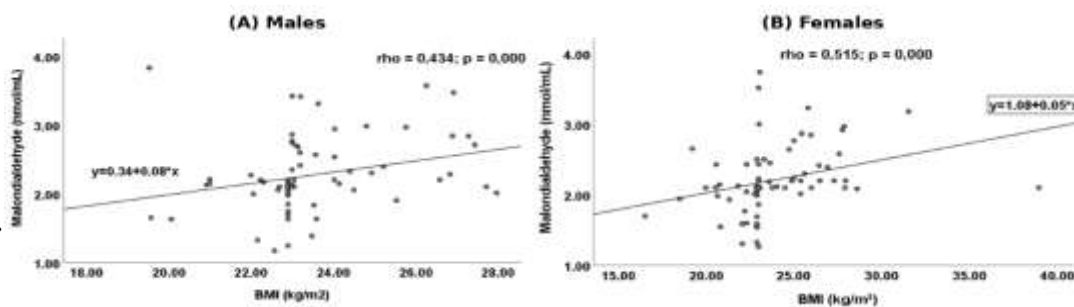


**Figure 2.**

type 2 diabetes mellitus

## 4. DISCUSSION

### 4.1. Study population and overall redox profile

Participants in the present study were aged 40–79 years, with a male-to-female ratio of 49.3% to 50.7%, which reduces the risk of bias when indices are compared between the sexes. The redox balance of this population was already displaced towards the pro-oxidant side. Mean plasma MDA ( $2.24 \pm 0.51$  nmol/mL) lay in the upper half of the reference interval for healthy adults (1.0–3.0 nmol/mL), whereas mean TAS ( $1.58 \pm 0.19$  mmol/L) fell in the lower-to-middle portion of the manufacturer's reference range. This combination of elevated lipid-peroxidation products with an unremarkable or depleted antioxidant reserve is consistent with the pooled estimates of the meta-analysis of 22 case-control studies cited above, in which MDA and nitric oxide were significantly higher, and glutathione and TAS significantly lower, in patients with T2DM than in controls [10].

### 4.2. Sex differences in TAS and MDA

Mean plasma TAS in men with T2DM ( $1.62 \pm 0.21$  mmol/L) was significantly higher than in women ( $1.54 \pm 0.15$  mmol/L;  $p = 0.011$ ). This result is comparable with that of Pawar et al. (2023), who reported a mean TAS of  $1.75 \pm 0.38$  mmol/L in patients with T2DM [21], and suggests that total antioxidant capacity tends to be better preserved in male than in female patients. Earlier studies have reported the same direction of difference and have attributed it to sex hormones, particularly oestrogen. Montoya-Estrada et al. (2020), comparing reproductive-aged with postmenopausal Mexican women, found markers of lipid peroxidation to be significantly higher after menopause [17]. The same pattern is observed when diabetes is present: Anklam et al. (2021), studying 64 women in the pre- and post-menopausal periods with and without T2DM, found that menopause and diabetes exerted synergistic effects on plasma lipoperoxidation, with post-menopausal diabetic women showing the highest lipoperoxidation levels of any group [16]. Women also tend to accumulate more visceral and subcutaneous fat, generating greater quantities of ROS through activation of NADPH oxidase, mitochondrial dysfunction, intracellular oxidative stress and chronic inflammation [22]. For MDA, the study found a statistically significant moderate positive correlation with BMI in both groups: men ( $\rho = 0.434$ ;  $p < 0.001$ ) and women ( $\rho = 0.515$ ;  $p < 0.001$ ). This indicates that the degree of lipid peroxidation tends to increase with increasing body mass index, reflecting a greater oxidative burden in obese patients with T2DM. The result is consistent with that of Das et al. (2016), who reported that MDA rose with the degree of obesity and correlated strongly and positively with BMI ( $r = 0.750$ ;  $p < 0.05$ ) in patients with T2DM [25]. In the present study, however, plasma MDA was not significantly correlated with waist circumference in either sex ( $p > 0.05$ ), which differs from the findings of the same authors, who observed a significant increase in MDA with waist circumference ( $r = 0.600$ ;  $p < 0.05$ ) [25].

Men generally have a larger muscle mass and use glucose and oxygen more efficiently, so that fewer ROS are generated for a given degree of hyperglycaemia. The total antioxidant reserve of women may therefore be consumed more rapidly in countering a higher ROS load. It should be noted, however, that under physiological conditions the opposite pattern is often described — women being less susceptible to oxidative stress owing to the antioxidant properties of oestrogen and to sex differences in NADPH-oxidase activity [15] — so that the direction observed here most plausibly reflects the predominantly post-menopausal age structure of our female participants (all aged  $\geq 40$  years) rather than an intrinsic sex effect.

In contrast, MDA concentration did not differ appreciably between the sexes ( $p = 0.488$ ), indicating a comparable degree of oxidative damage in men and women in this cohort. Our value is somewhat lower than that reported by Pawar et al. (2023), in which plasma MDA was  $3.92 \pm 1.85$   $\mu$ mol/L [21]. The dissociation between the two markers is itself informative: it suggests that at an equivalent level of oxidative injury, women in this population maintained a smaller antioxidant reserve, and therefore a narrower margin of protection, than men.

### 4.3. Associations with metabolic indices

When the relationship between oxidative stress, expressed as TAS and MDA, and key metabolic indices — fasting plasma glucose, BMI and waist circumference — was examined, plasma TAS showed a statistically significant weak inverse correlation with BMI in men ( $\rho = -0.305$ ;  $p = 0.008$ ) and in women ( $\rho = -0.338$ ;  $p = 0.003$ ). This finding accords with that of Al-Salman et al. (2025), who likewise observed that TAS declined as BMI increased [23], and with the systematic review and meta-analysis of Anaya-Morua et al. (2023) on total antioxidant capacity and anthropo-metabolic markers in obese and non-obese subjects [24]. By contrast, no significant correlation was found between TAS and fasting plasma glucose or waist circumference in either sex, indicating that TAS does not directly reflect either the prevailing plasma glucose concentration or waist circumference.

### 4.4. Comparison with international data

Direct comparison of absolute TAS and MDA values across studies is hampered by methodological heterogeneity. Antioxidant capacity is variously reported as TAS, TAC, FRAP or ORAC; MDA is measured as free MDA, as TBARS or by immunoassay; and the units in circulation differ by up to three orders of magnitude (Table 4). Absolute concentrations should therefore be interpreted within, rather than across, assay platforms. What can legitimately be compared is the direction and pattern of association, and on that criterion the present findings align closely with the recent international literature.

**Table 4.** Comparison of the present findings with recent international studies of oxidative stress markers in type 2 diabetes mellitus

| Study                            | Country       | Population                                          | Antioxidant index                 | MDA                                                                        | Association with adiposity                                            |
|----------------------------------|---------------|-----------------------------------------------------|-----------------------------------|----------------------------------------------------------------------------|-----------------------------------------------------------------------|
| Present study                    | Vietnam       | 140 T2DM outpatients, 40–79 y                       | TAS $1.58 \pm 0.19$ mmol/L        | $2.24 \pm 0.51$ nmol/mL (= $2.24 \mu\text{mol/L}$ )                        | TAS ↓ and MDA ↑ with BMI in both sexes; no association with FPG or WC |
| Pawar et al., 2023 [21]          | India         | T2DM patients                                       | TAS $1.75 \pm 0.38$ mmol/L        | $3.92 \pm 1.85$ $\mu\text{mol/L}$                                          | Not reported                                                          |
| Abu Khadra et al., 2024 [12]     | Jordan        | 201 T2DM, 90 obese, 115 non-obese controls          | Not measured (catalase ↓ in T2DM) | $0.230 \pm 0.05$ vs $0.207 \pm 0.06$ vs $0.135 \pm 0.04$ $\mu\text{mol/L}$ | MDA raised by obesity almost to diabetic levels                       |
| Das et al., 2016 [25]            | Romania       | T2DM patients                                       | Not reported                      | ↑ with degree of obesity                                                   | MDA–BMI $r = 0.750$ ; MDA–WC $r = 0.600$ ( $p < 0.05$ )               |
| Al-Salman et al., 2025 [23]      | Iraq          | T2DM case–control                                   | TAS ↓ vs controls                 | Not reported                                                               | TAS declines as BMI rises                                             |
| Cecerska-Heryć et al., 2025 [13] | Poland        | 40 T2DM, 33 T1DM, 41 controls                       | SOD, GPX1, CAT altered            | Not reported                                                               | BMI, treatment type and complications all modify redox markers        |
| El Frakchi et al., 2024 [14]     | Morocco       | 254 T2DM outpatients                                | Dietary TAC                       | Not measured                                                               | Dietary TAC inversely associated with BMI, WC and fat mass            |
| Banik & Ghosh, 2021 [10]         | Meta-analysis | 22 case–control studies; 1,667 T2DM, 1,186 controls | TAS and GSH ↓ in T2DM             | ↑ in T2DM (SMD 2.27)                                                       | Not assessed                                                          |

TAS: total antioxidant status; TAC: total antioxidant capacity; MDA: malondialdehyde; FPG: fasting plasma glucose; WC: waist circumference; SMD: standardised mean difference; SOD: superoxide dismutase; GPX1: glutathione peroxidase 1; CAT: catalase. Absolute values are not directly comparable across studies because of differences in analytical method, matrix and units. MDA values are expressed in  $\mu\text{mol/L}$  throughout the table for comparability;  $2.24 \text{ nmol/mL}$  is numerically identical to  $2.24 \mu\text{mol/L}$ , and the present study's value is reported in nmol/mL in Table 2 and in the text.

Our mean TAS of  $1.58 \pm 0.19$  mmol/L is modestly lower than the  $1.75 \pm 0.38$  mmol/L reported by Pawar et al. using the same ABTS principle, while our mean MDA of  $2.24 \pm 0.51$  nmol/mL, equivalent to  $2.24 \mu\text{mol/L}$ , is appreciably lower than their  $3.92 \pm 1.85 \mu\text{mol/L}$  [21]. In redox terms the two differences point in opposite directions, a smaller antioxidant reserve but less lipid peroxidation, which illustrates the difficulty of cross-laboratory comparison and argues for interpreting each cohort against its own reference interval rather than against absolute values reported elsewhere. What is reproducible is the pattern: pooled  $\mu\text{mol/L}$  [12]. That obesity alone raises lipid peroxidation almost to diabetic levels supports our observation that, within a diabetic population, it is adiposity rather than glycaemia that grades the oxidative burden. Cecerska-Heryć et al. (2025), studying 40 patients with T2DM, 33 with type 1 diabetes and 41 controls, likewise found that BMI, treatment modality and the presence of complications each modified antioxidant enzyme activity and inflammatory markers [13]; this reinforces both our

data across 22 case–control studies confirm that MDA is raised and TAS and glutathione depressed in T2DM relative to healthy subjects [10], and our values sit within that pattern.

Two recent studies bear particularly directly on our central finding. The Jordanian cross-sectional study of 406 adults separated the contribution of diabetes from that of adiposity, showing that serum MDA in obese non-diabetic individuals ( $0.207 \pm 0.06 \mu\text{mol/L}$ ) approached that of patients with T2DM ( $0.230 \pm 0.05 \mu\text{mol/L}$ ) and clearly exceeded that of non-obese healthy controls ( $0.135 \pm 0.04$

BMI finding and our recognition that failure to stratify by treatment regimen is a genuine limitation of the present analysis. A convergent line of evidence comes from the nutritional side. El Frakchi et al. (2024) reported in 254 Moroccan outpatients with T2DM a population with a comparable burden of overweight and obesity to ours — that dietary total antioxidant capacity was inversely associated with BMI, waist circumference and fat mass percentage independently of the

confounders assessed [14]. Our finding of a circulating counterpart, plasma TAS falling as BMI rises, closes the loop between antioxidant intake and antioxidant status within the same clinical population and suggests that the two measures capture complementary aspects of the same process.

Where our results depart from the literature, the divergences are informative rather than contradictory. Our MDA–BMI correlations were moderate ( $\rho$  0.434–0.515) against the strong association ( $r$  = 0.750) reported by Das et al., and we detected no MDA–waist association where they reported one ( $r$  = 0.600) [25]. Differences in sample characteristics, degree of glycaemic control, degree of obesity and fat distribution between populations, together with the narrower BMI range of a predominantly Asian cohort classified by the WHO Asian cut-offs, are the most plausible explanations. Finally, sex-stratified analyses of paired oxidant and antioxidant markers remain BMI increased, in both sexes. The reciprocity of these associations is important, because it indicates not the random fluctuation of a single analyte but a coordinated displacement of the redox equilibrium, in which greater adiposity is accompanied both by greater oxidative damage and by diminished antioxidant buffering. Since MDA and TAS were measured by independent analytical principles — TBA-adduct spectrophotometry and ABTS® decolourisation, respectively — the convergence of the two gradients on BMI strengthens this inference. Third, the metabolic variable that carried the association was adiposity rather than glycaemia: neither marker correlated significantly with fasting plasma glucose in either sex.

Mechanistically, this pattern is what current models of the obesity–oxidative stress–insulin resistance triad predict. As adipose tissue expands, increased non-esterified fatty acid flux activates NADPH oxidase while the expression of antioxidant enzymes (superoxide dismutase, catalase and glutathione peroxidase) is suppressed, so that ROS generation rises selectively within the fat depot. Furukawa et al. demonstrated that this local redox shift precedes and drives the dysregulated secretion of adipocytokines — falling adiponectin and rising plasminogen activator inhibitor-1, interleukin-6 and monocyte chemoattractant protein-1 — that characterises the metabolic syndrome, and proposed that oxidative stress in accumulated fat is an early instigator rather than a late consequence of metabolic disease [7]. Reactive oxygen species in turn interfere with proximal insulin signalling, both through stress-activated kinases (JNK, IKK $\beta$  and p38 MAPK) that phosphorylate insulin receptor substrate-1 on serine residues and through mitochondrial overproduction of superoxide under conditions of substrate surplus, thereby reducing GLUT4-mediated glucose uptake in skeletal muscle and adipose tissue [8]. Hyperglycaemia then feeds back into the same pathways [5]. On this reading, oxidative stress is not merely a consequence of diabetes but a plausible shared upstream mechanism — the "common soil" proposed by Ceriello and Motz to link insulin resistance,  $\beta$ -cell dysfunction and endothelial injury [6]. Our data are cross-sectional and cannot establish direction of causation, but they are consistent with adiposity being the

uncommon in the recent literature, which reports sex differences in redox biology largely in cardiovascular rather than diabetic populations [15] or in menopausal rather than mixed-sex cohorts [16]; the present data therefore add to a sparse evidence base.

#### 4.5. Oxidative stress as a link between adiposity and metabolic dysregulation

Taken together, the present findings address the central research question — what role oxidative stress plays in the metabolic disturbances of patients with T2DM — through three connected observations. First, the population studied was already in a pro-oxidant state, with high-normal lipid peroxidation and a modest antioxidant reserve. Second, the two markers moved in opposite directions with respect to the same metabolic variable: TAS fell and MDA rose as

principal driver of this process in outpatients whose diabetes is already pharmacologically treated.

#### 4.6. Why adiposity, rather than a single fasting glucose value, tracked oxidative stress

The absence of any correlation between the redox markers and fasting plasma glucose deserves comment, since a simple model would predict one. Fasting plasma glucose is a point-in-time measurement, whereas the oxidative burden relevant to lipid peroxidation is cumulative and depends on chronic glycaemic exposure, glycaemic variability and postprandial excursions rather than on a single fasting value. Adiposity, by contrast, is a stable and integrating exposure, a standing source of ROS that does not fluctuate from hour to hour. In addition, all participants were receiving insulin, metformin, or both. Metformin has documented antioxidant properties that are partly independent of its glucose-lowering action, operating through AMP-activated protein kinase activation, partial inhibition of mitochondrial complex I and enhancement of endogenous antioxidant enzyme activity; a randomised trial in newly diagnosed T2DM reported significant reductions in oxidation products and improvement in antioxidant reserve with metformin compared with lifestyle modification alone [26]. Treatment may therefore have compressed the variance in both glycaemia and redox markers and attenuated any residual correlation. A similar argument applies to waist circumference, which correlated with neither marker: in a population in which more than half of the participants were overweight or obese, tape measurement of waist circumference may discriminate visceral adiposity less sharply than BMI and is subject to greater measurement error.

#### 4.7. Clinical implications

Two practical points follow. First, weight management in T2DM should be regarded not only as a glycaemic intervention but also as an antioxidant one. Because BMI and not fasting glucose was the metabolic index most consistently coupled to redox status in this cohort, reducing adiposity may be the most accessible means of lowering the oxidative burden in patients already receiving glucose-lowering therapy; the parallel observation that higher dietary antioxidant capacity

accompanies lower BMI and waist circumference in T2DM outpatients [14] suggests that dietary and anthropometric strategies act on the same axis. Second, because women showed a lower total antioxidant reserve at an equivalent level of lipid peroxidation, post-menopausal female patients may warrant particular attention in nutritional counselling aimed at increasing antioxidant intake — a group in which menopause and diabetes have been shown to act synergistically on lipoperoxidation [16]. These observations also define a rational framework for future interventional research: trials of antioxidant supplementation or antioxidant-rich dietary patterns in T2DM should stratify by adiposity and by sex, and should use paired oxidant and antioxidant markers rather than either alone, since the present data show that the two indices carry complementary information.

#### 4.8. Limitations

Several limitations should be acknowledged. Patients were treated with insulin, metformin, or a combination of the two, but the analysis did not stratify by treatment group in order to exclude this potential confounder of oxidative status — a factor shown to matter in recent work [13]. Although patients with established complications were excluded, diabetes duration was not an exclusion criterion and was not adjusted for. Owing to budgetary constraints, HbA1c — the standard index of glycaemic control and treatment response — was not measured, which may have introduced substantial confounding; the absence of a correlation between the redox markers and fasting plasma glucose must therefore be interpreted with caution, since a single fasting value is a poor surrogate for chronic glycaemic exposure. The cross-sectional design and the use of convenience sampling at a single centre preclude causal inference and limit generalisability, and the absence of a non-diabetic control group means that the degree of redox displacement relative to the healthy Vietnamese population could not be quantified — a comparison for which no published Vietnamese reference data currently exist. Dietary antioxidant intake, smoking status and physical activity, all recognised determinants of TAS and MDA, were likewise not recorded. These limitations define the gaps that future studies should address in order to improve the reliability of the findings.

#### 5. CONCLUSION

In patients with type 2 diabetes mellitus, total antioxidant status was better preserved in men than in women. Markers of oxidative stress (TAS and MDA) were associated with overweight and obesity. The reciprocal behaviour of the two markers with respect to BMI — falling antioxidant capacity alongside rising lipid peroxidation — indicates that oxidative stress in T2DM is coupled most closely to adiposity rather than to prevailing fasting glycaemia, and supports the view that redox imbalance is an integral component of, rather than merely a consequence of, the metabolic disturbance of type 2 diabetes. These are, to our knowledge, the first paired plasma TAS and MDA data reported in Vietnamese patients with T2DM, and they provide a basis for interventional studies stratified by adiposity and by sex.

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