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Biochemical Markers in Adults with Metabolic Syndrome, Insulin Resistance, Oxidative Stress, and Inflammation

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Abstract

This cross-sectional study includes 120 adults, 60 with metabolic syndrome MetS and 60 controls. Also, involved the relationship between insulin resistance, inflammation, and oxidative stress. The MetS group showed higher levels of BMI, waist circumference, blood pressure, fasting glucose, insulin, HOMA-IR, triglycerides, MDA, and hs-CRP, and lower levels of HDL cholesterol, TAC, and adiponectin ($p < 0.001$). A positive correlation was found between HOMA-IR and MDA/hs-CRP, and a negative correlation with TAC/adiponectin. Path analysis revealed that BMI indirectly influenced HOMA-IR via MDA and hs-CRP ($\beta = 0.34$, $p < 0.001$). A combined biomarker panel (MDA, TAC, hs-CRP, adiponectin) showed high diagnostic performance (AUC = 0.91). The study suggests that oxidative stress, inflammation, and decreased adiponectin are closely linked to insulin resistance in MetS, highlighting their potential for improved risk stratification.

Keywords: Metabolic Syndrome, Oxidative Stress, and Malondialdehyde.

1. Introduction

Metabolic syndrome (MetS) is a multifactorial disorder that is characterized by central obesity, dyslipidemia, glucose dysregulation, hypertension, endothelial dysfunction, and cardiometabolic harm [1, 2]. These mechanisms are the result of overload of nutrients, growth of adipocytes, dysfunction of mitochondria, and redox imbalance and culminate in the reactive oxygen species, lipid peroxidation, insulin signaling impairment, and chronic inflammation, transforming MetS into a metabolic phenotype into a systemic disease with extensive manifestations [3, 4].

Adiponectin is an adipokines and inflammatory proteins that are involved in these processes. Adiponectin enhances insulin sensitivity, lipid burning, and decreases inflammation, and its malfunction is associated with obesity and MetS [5, 6]. There are also inflammatory indicators such as hs-CRP that are also significant in foretelling MetS and the risks [7, 8]. Recent research has proposed that the integration of oxidative stress markers, hs-CRP, adiponectin and insulin resistance into one model can improve the power of differentiating MetS [9-11]. This research paper was designed to explore how these biomarkers are altered in the presence of MetS. Besides, correlate with a blood test-based insulin resistance index called Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) that utilizes fasting glucose and fasting insulin levels to assess insulin resistance [10, 11].

MetS has acquired pandemic levels of prevalence, with its impact on the adult population of the world approximately a quarter of the increasing prevalence of obesity and sedentary lifestyles [12, 13]. This growing burden leaves a heavy load in terms of the health care of the population because people with MetS are under a high risk of having type 2 diabetes mellitus and cardiovascular disease. The early detection and treatment can be regarded as a primary clinical concern [14, 15]. Although the traditional diagnostic criteria of MetS are useful in terms of their ability to reflect the clustering of the core components of the syndrome. They are frequently inadequate in their attempts to reflect the complex pathophysiological hierarchy underlying the syndrome. In particular, the conventional parameters are not measured in quantifying the extent of systemic oxidative stress or the low-grade chronic inflammation that are the major contributors of the endothelial dysfunction and insulin resistance, which may postpone intervention until the metabolic derangements have taken root [16, 17].

As a result, there is a need to shift to a paradigm that is more pathophysiology oriented. The main stimulus is visceral adiposity that leads to a metabolic state of meta flammation, where the dysfunctional adipose tissue secretes less protective adiponectin and more pro-inflammatory cytokines [18]. This disequilibrium creates a vicious cycle in which oxidative stress and inflammation increase each other’s insulin resistance further enhancing the progression of risk factors cluster to a system-wide disease [19, 20]. That is why only one

biomarker would not be enough, a combination of adiponectin, hs-CRP, and HOMA-IR can provide a more effective tool to measure the severity of the disease and isolate individuals with high risks.

2. Methodology

2. 1 Study Design and Participants

A cross-sectional study design was utilized and included 120 adults between 30 and 60 years. Half of them were healthy adults (control group) and the other half met the criteria of metabolic syndrome (MetS group). This separation was used to compare biochemical and clinical markers in the two groups [12].

2. 2 Inclusion Criteria

The criteria used to classify participants of the MetS group were current metabolic syndrome, where three or more of the following must be present. Increased waist circumference (abdominal obesity), high levels of fasting blood glucose (insulin resistance), high levels of triglycerides (lipid imbalance). Low levels of HDL-cholesterol (increased cardiovascular risk) and high blood pressure (increased risk of heart disease and stroke). These are factors that are used to diagnose the metabolic syndrome and determine the associated health risks [13, 14].

2. 3 Exclusion Criteria

Certain conditions were omitted, patients who had Type 1 diabetes, chronic inflammatory disease, chronic kidney disease, liver failure, malignancies, acute infections, antioxidant supplementation or were pregnant were excluded as these may modify the metabolic and inflammatory indicators and confound the results of the study [15].

2. 4 Samples Collection

Each subject was sampled in an 8 mL of venous blood, after 10-12 hours of fast. All samples were separated into lipid profile, hs-CRP, adiponectin, and oxidative stress marker serum tubes, fasting glucose fluoride tubes, and insulin assays in EDTA incubated tubes. Centrifuging of the blood was done at a speed of 3000 rpm, where it was centrifuged within 10 minutes until the serum and plasma were stored at -20 °C [16].

2. 5 Biochemical Assays

The research quantified the vital parameters with the help of numerous biochemical techniques. The enzymatic colorimetric method was the method used in the determination of fasting blood glucose (FBG), triglycerides, HDL cholesterol, and

total cholesterol, which were measured using enzymatic spectrophotometry [17].

The ELISA method was used to determine the level of fasting insulin and the TBARS method to determine the level of malondialdehyde (MDA). The Trolox-equivalent method was used to evaluate the total antioxidant capacity (TAC). The level of C-reactive protein was used as a marker of high sensitivity, and adiponectin concentration was measured using the sandwich ELISA [8, 18].

2. 6 Insulin Resistance Determination

The insulin resistance was estimated using the HOMA-IR formula [11].

$$\text{HOMA-IR} = \text{Fasting glucose (mg/dL)} \times \text{Fasting insulin (μIU/mL)} / 405$$

2. 7 Statistical Analysis

SPSS version 26 and AMOS structural equation modeling (SEM) were used to analyze data. Continuous variables were reported in the form of mean ± standard deviation and group difference in the form of independent samples t-tests. Pearson Correlations were applied to test the relationship between biomarkers [19].

Multivariate logistic regression was conducted and adjusted on age, sex and BMI, to measure predictions of independent variables on MetS [20]. The mediation model was tested through path analysis that BMI has a direct and indirect effect on HOMA-IR through MDA and hs-CRP [3]. CFI, RMSEA and SRMR were used to assess model fit. Comparison of diagnostic performance of biomarkers was done by ROC analysis, and the calibration of the combined model was determined through the Hosmer-Lemeshow test [21]. Sensitivity analysis was done without outliers more than 3 standard deviations [22]. A p-value of less than 0.05 was taken as significant.

3. Results and Discussion

3. 1 Baseline Characteristics

MetS group exhibited significantly higher levels of BMI, waist circumference, systolic and diastolic blood pressure compared to the control group as shown in table 1.

Table 1: Anthropometric and clinical characteristics of the study population.

Variable	Control (n = 60)	MetS (n = 60)	p-value
Age (years)	44.3 ± 7.8	45.6 ± 8.1	0.381
BMI (kg/m²)	24.1 ± 2.3	32.8 ± 3.9	< 0.001
Waist circumference (cm)	84.6 ± 7.4	107.2 ± 9.1	< 0.001
Systolic BP (mmHg)	117.4 ± 10.2	142.6 ± 12.5	< 0.001
Diastolic BP (mmHg)	75.8 ± 7.3	89.4 ± 8.6	< 0.001

Table 1 shows that the MetS group had significantly higher BMI, WC, SBP and DBP than the control group ($p < 0.001$). These results are not surprising, as the metabolic syndrome is associated with the presence of central obesity and hypertension as key diagnostic features. However, age did not significantly affect the groups, suggesting that the changes seen were due more to metabolic syndrome than to aging [2, 12].

3. 2 Biochemical Findings

The biochemical parameters presented in table 2 indicate elevated levels of fasting glucose, insulin, triglycerides, MDA, hs-CRP, and reduced levels of HDL cholesterol and adiponectin in the MetS group.

Table 2: Biochemical parameters in control and metabolic syndrome groups.

Variable	Control (n = 60)	MetS (n = 60)	p-value
Fasting glucose (mg/dL)	89.1 ± 8.4	121.0 ± 16.8	< 0.001
Fasting insulin (µIU/mL)	8.7 ± 2.1	18.9 ± 5.4	< 0.001
HOMA-IR	1.91 ± 0.56	5.64 ± 1.73	< 0.001
Triglycerides (mg/dL)	118.5 ± 28.7	224.6 ± 51.2	< 0.001
HDL-C (mg/dL)	54.2 ± 8.3	38.1 ± 6.7	< 0.001
MDA (nmol/mL)	2.10 ± 0.48	4.72 ± 0.91	< 0.001
TAC (mmol Trolox/L)	1.58 ± 0.26	0.96 ± 0.22	< 0.001
hs-CRP (mg/L)	1.32 ± 0.64	4.83 ± 1.56	< 0.001
Adiponectin (µg/mL)	9.84 ± 2.11	5.08 ± 1.44	< 0.001

Biochemical changes seen in the MetS group are consistent with those expected since MetS has been linked with obesity related insulin resistance, chronic low-grade inflammation and oxidative stress. Visceral fat releases free fatty acids and pro-inflammatory cytokines, disrupts insulin signaling and leads to hyperglycemia and hyperinsulinemia.

The pathogenesis of dyslipidemia is the result of defective lipid metabolism manifested as increased blood triglycerides and decreased HDL-cholesterol. Oxidative stress is associated with a decrease in antioxidant defenses (TAC) and an increase in lipid peroxidation (MDA). Moreover, inflammatory activation increases levels of

hs-CRP and adiponectin decreases due to adipose tissue dysfunction, which prevents its release. All these mechanisms are responsible for the biochemical profile seen in the MetS group and are like those reported earlier [5, 9].

3. 3 Correlation Analysis

A positive correlation between HOMA-IR and MDA/hs-CRP and a negative correlation with TAC/adiponectin were listed in table 3.

Table 3: Correlation of HOMA-IR with selected biochemical markers.

Variable	r-value	p-value
MDA	+0.61	<0.001
TAC	-0.53	<0.001
hs-CRP	+0.57	<0.001
Adiponectin	-0.49	<0.001
Triglycerides	+0.55	<0.001
HDL-C	-0.46	<0.001

Oxidative stress contributes to the rise of MDA level, resulting in lipid peroxidation and cell damage, while the chronic low-grade inflammation leads to the rise of production of hs-CRP. Insulin resistance also increases hepatic triglyceride synthesis and decreases lipid utilization leading to hypertriglyceridemia. TAC, adiponectin and HDL-C, on the other hand, exhibited negative correlation with HOMA-IR, indicating they have protective metabolic and anti-inflammatory effects.

Low levels of antioxidant capacity (TAC) is an indicator of diminished antioxidant defenses during periods of oxidative stress, and low adiponectin levels are associated with decreases in insulin sensitivity and increased inflammation. Likewise, HDL-C has anti-inflammatory and antioxidant properties, and lower HDL-C levels are often linked to increased insulin resistance and metabolic abnormalities [10, 23].

3. 4 Multivariable Regressions

MDA and hs-CRP were identified as independent predictors of MetS after adjusting for age, sex, and BMI as listed in table 4.

Table 4: Multivariable logistic regression for predictors of metabolic syndrome (adjusted for age, sex, and BMI).

Predictor	Adjusted OR	95% CI	p-value
MDA (per 1 nmol/mL increase)	2.36	1.55-3.59	< 0.001
TAC (per 1 mmol/L increase)	0.21	0.09-0.48	< 0.001
hs-CRP (per 1 mg/L increase)	1.41	1.16-1.71	0.001
Adiponectin (per 1 µg/mL increase)	0.72	0.60-0.87	0.001

All biomarkers demonstrated significant differences between the control and MetS groups in the univariate analysis. The multivariable logistic regression was also performed to assess if these biomarkers were independently associated with MetS after controlling for potential confounding factors including age, sex, and BMI.

Results of the regression showed that both MDA and hs-CRP had a positive predictive effect with higher levels being associated with greater odds of MetS (Adjusted OR >1). Conversely, TAC and adiponectin had Adjusted OR values < 1, which indicate a protective effect against MetS. Therefore, the statement is about the direction and magnitude of the modified regression relationships, not to the mean differences between groups displayed in the table.

3. 5 Path Analysis and Structural Equation Modeling.

Structural equation modeling (SEM) was used to assess the direct and indirect effects of obesity (BMI) on insulin resistance (HOMA-IR) via oxidative stress (MDA) and inflammation (hs-CRP). The hypothesized model demonstrated a good fit (CFI = 0.94, RMSEA = 0.06, SRMR = 0.05). BMI showed a significant direct effect on HOMA-IR (β = 0.42, p = 0.001) and indirect effects mediated through MDA (β = 0.19, p = 0.002) and hs-CRP (β = 0.15, p = 0.004), with a total indirect effect of β = 0.34 (p < 0.001). The results indicate that the obesity/IR relationship is mediated, in part, through oxidative stress and inflammation [3, 4].

3. 6 Sensitivity Analysis

Omission of outliers (n = 4) did not have a significant difference in findings. Adjusted ORs of MDA (2.28, 95% CI: 1.48-3.51), hs-CRP (1.38, 95% CI: 1.12-1.68), TAC (0.23, 95% CI: 0.10-0.51) and adiponectin (0.74, 95% CI: 0.61-0.89) were all significant and the strength of the findings was confirmed [22]. Levels of oxidative stress markers in both the control and MetS groups, highlighting the increased levels in the MetS group, are shown in figure 1.

The correlation pattern between HOMA-IR and major biomarkers, demonstrating significant positive and negative associations are demonstrated in figure 2. While, ROC performance of individual and combined biomarkers for MetS detection shown in figure 3.

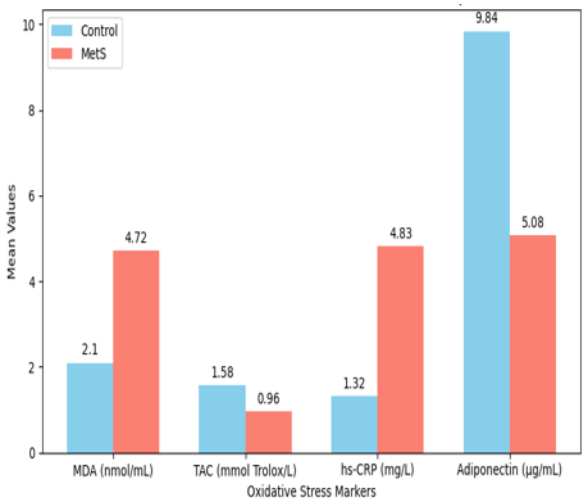

Figure 1: Mean oxidative stress marker levels in control and MetS groups.

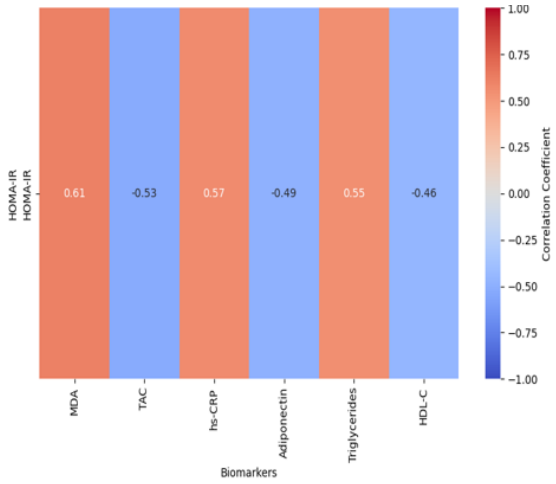

Figure 2: Correlation pattern between HOMA-IR and major biomarkers.

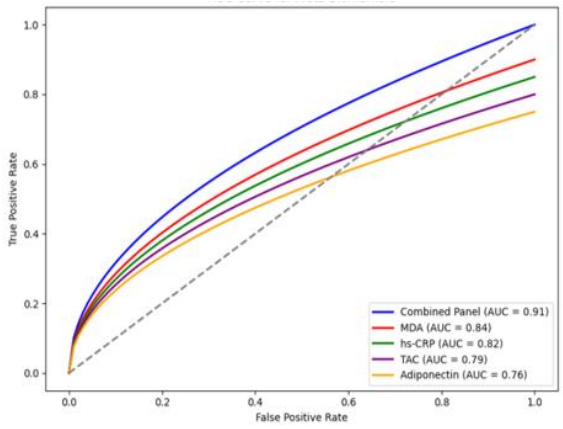

Figure 3: ROC performance of individual and combined biomarkers for MetS detection.

The ability of the biomarker panel to identify metabolic syndrome was excellent. Several biomarkers measure different pathophysiological components of the metabolic syndrome at once such as oxidative stress (MDA), antioxidant defense (TAC), inflammation (hs-CRP) and adipose tissue dysfunction (adiponectin). The model showing the summation of all individual biomarkers is more sensitive and more specific for determining the status of the disease, as it gives a better picture of disease status than the individual biomarkers.

This is evidenced by the combined panel having a higher AUC (0.91) than any individual biomarker including MDA (0.84), hs-CRP (0.82), TAC (0.79) and adiponectin (0.76). Thus, the overall accuracy of the detection of MetS is enhanced by considering

the combined biomarker approach, as demonstrated before in figure 3 [21, 23]. The biochemical profile of the study helps to support the opinion that MetS is a redox imbalance, adipose tissue inflammation, and insulin signaling disorder [1, 3]. The high MDA and low TAC levels of the MetS group are associated with the obesity-induced oxidative stress and lipid peroxidation conditions that interfere with the insulin signal [10, 18].

MDA is an adulator to insulin receptors and IRS-1 which interferes with insulin transmission and favors resistance [10]. There will also be increased hs-CRP in MetS since inflammation contributes significantly to insulin resistance [24]. Reduced levels of adiponectin that possess anti-inflammatory and insulin-sensitizing properties are also additional contributors of MetS [5-7]. Establish the relationship between BMI and HOMA-IR, path analysis indicates that the effect of BMI in using oxidative stress and inflammation, implying that the possibility to alleviate the effects of obesity on metabolism is to control these two variables [2, 3].

Multi-markers (MDA, TAC, hs-CRP, adiponectin) are better than single markers in the diagnosis of MetS [21, 23]. The relevance of biochemical monitoring is supported in intervention studies, and lifestyle changes and supplements demonstrate the possible advantages of oxidative stress and inflammation in MetS [25].

4. Conclusion

Biochemical changes among adults with metabolic syndrome are characterized by an increased level of lipid peroxidation, a lower antioxidant capacity, inflammation, a lower level of adiponectin, and insulin resistance. Path analysis shows that the interaction between obesity and insulin resistance is mediated by oxidative stress and inflammation. The assimilation of MDA, TAC, hs-CRP and adiponectin provide a sound framework of diagnosing MetS that can be utilized in the early diagnosis, metabolic profiling, and monitoring interventions. Further research is required on how these biomarkers change over time and how can be used during personalized therapy.

5. References

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