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Coronary Microvascular Dysfunction and Normoglycemic Insulin Resistance: The Invisible Threat

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Abstract **Original Research Article**

This study aims to investigate the presence and associated factors of Coronary Microvascular Dysfunction [CMD] in young women who presented to the hospital with dyspnea, chest pain, and hypertension, and who were non-diabetic but exhibited insulin resistance. Our findings reveal that insulin resistance is a significant risk factor for CMD in young women, even when their blood sugar levels are normal [normoglycemic]. Notably, the increased epicardial fat thickness observed in these patients suggests that it may play a critical role in the pathophysiology of CMD. These results emphasize the need to consider metabolic parameters for the early diagnosis and treatment of CMD in young and normoglycemic individuals.

Keywords: Coronary Microvascular Dysfunction, insulin resistance, normoglycemic, metabolic syndrome, Homeostatic Model Assessment of Insulin Resistance, Leptin/Adiponectin, Transthoracic ECHO, Endothelial Function.

INTRODUCTION

Coronary Microvascular Dysfunction [CMD] is strongly associated with components of the metabolic syndrome, such as diabetes and obesity, and is a significant predictor of increased cardiovascular risk in these diseases [1,2,3,4,5]. However, less information is available regarding the prevalence and underlying pathophysiological mechanisms of CMD in young women who have normal blood sugar levels [normoglycemia] but exhibit insulin resistance. It has been shown that insulin resistance can trigger endothelial dysfunction and initiate the process of subclinical atherosclerosis even before glucose levels become impaired [6,7,8,9,10,11]. It is hypothesized that in this population, insulin resistance poses an invisible threat, leading to damage at the microvascular level. In this study, we aimed to shed light on this important issue in normoglycemic young women by evaluating the Homeostatic Model Assessment of Insulin Resistance [HOMA-IR], the leptin-to-adiponectin ratio, epicardial fat thickness, and coronary flow reserve [CFR]. The leptin/adiponectin ratio has been suggested as a powerful marker of insulin resistance and associated cardiovascular risk [12,13,14]. Furthermore, we tested the hypothesis that an increase in epicardial fat tissue thickness may directly affect the coronary microvascular bed through local inflammation and vascular dysfunction [15,16,17,18,19]. A reduction in coronary flow reserve is accepted as an early and important indicator of microvascular dysfunction [20,21,22].

METHODS

The study included a total of 24 young female patients with an abnormal Coronary Flow Reserve [CFR] who were also normoglycemic. Measurements for all patients were recorded, including age, BMI, leptin/adiponectin ratio, endothelial function of the brachial artery [FMD], and epicardial adipose tissue [EAT] thickness.

Table 1: Measurement Protocols

Parameter	Method
Insulin Resistance	HOMA-IR [Formula: [Glucose [mg/dL] x Insulin [µIU/mL]] / 405]
CFR [Coronary Flow Reserve]	Adenosine-stress echocardiography [LAD end-diastolic flow velocity]
Epicardial Fat	Transthoracic ECHO [Right ventricle free wall, end-diastole]
Endothelial Function	Brachial artery FMD [Flow-Mediated Dilation]
Biomarkers	ELISA [Leptin, Adiponectin, hs-CRP]

FINDINGS

Out of the 24 patients, both the CFR [Coronary Flow Reserve] and HOMA-IR values were abnormal in 18 patients. In 15 of these patients, the brachial artery Flow-Mediated Dilation [FMD] was defined as below 7% [Figure 1], while in 9 patients, it was between 10-15%. The 15 individuals with FMD below 7% were found to have a CFR below 2 and a HOMA-IR value above 2. Thus, in 15 of the 18 patients with abnormal CFR and HOMA-IR, the brachial artery Flow-Mediated Dilation was also detected as abnormal. In all 24 patients, the leptin/adiponectin ratio was abnormal and the Epicardial Adipose Tissue [EAT] thickness was increased. The average BMI was found to be 29.8. In 6 patients, the CFR was abnormal despite having normal HOMA-IR values. However, the leptin/adiponectin ratio was also abnormal and the EAT thickness was increased in most of these patients. This suggests that microvascular dysfunction may be associated not only with insulin resistance but also with other metabolic factors.

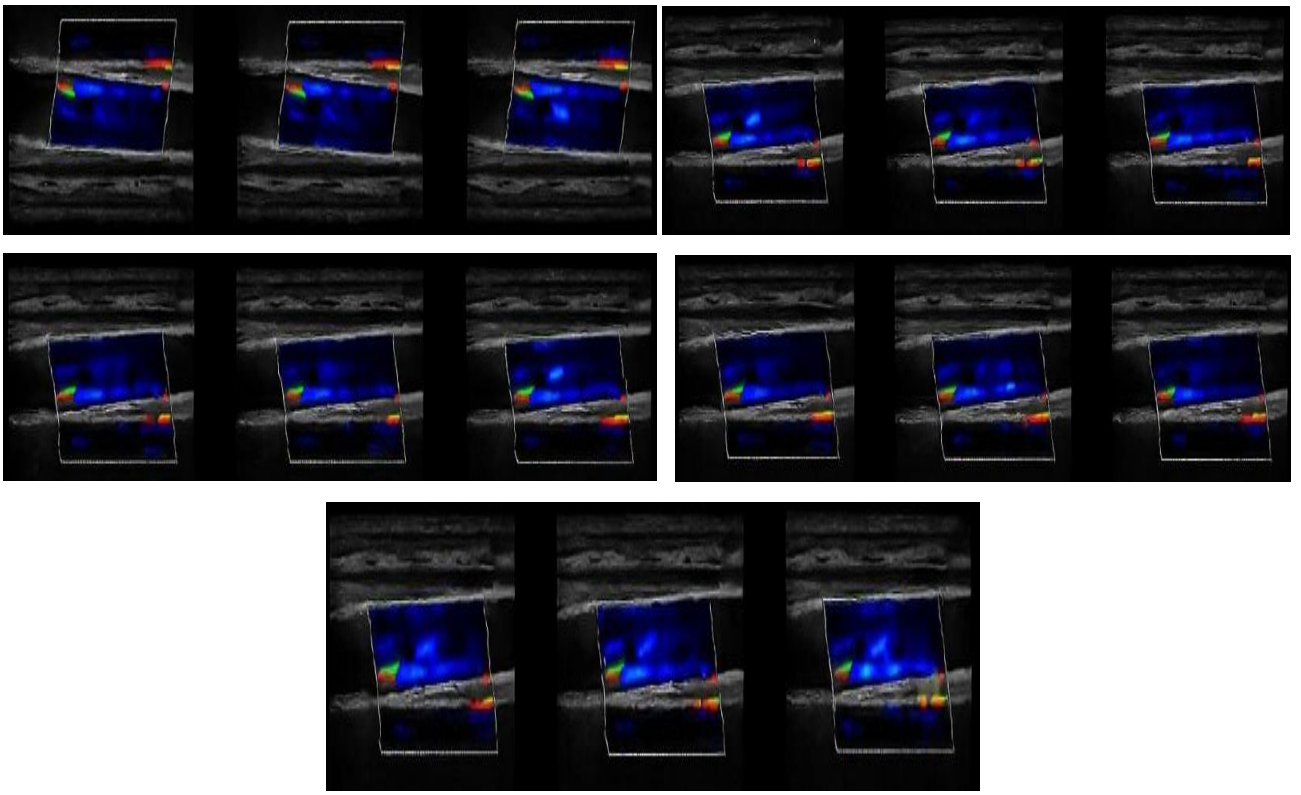
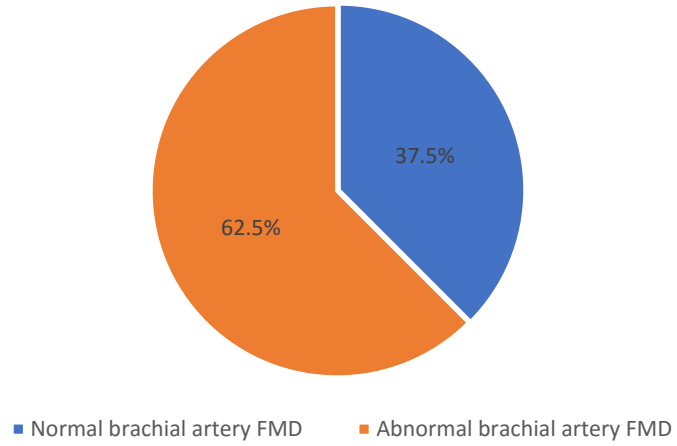


Figure-1



Graph 1. Of 24 patients, 15 [62.5%] exhibited abnormal brachial artery FMD, and 9 exhibited normal brachial artery FMD.

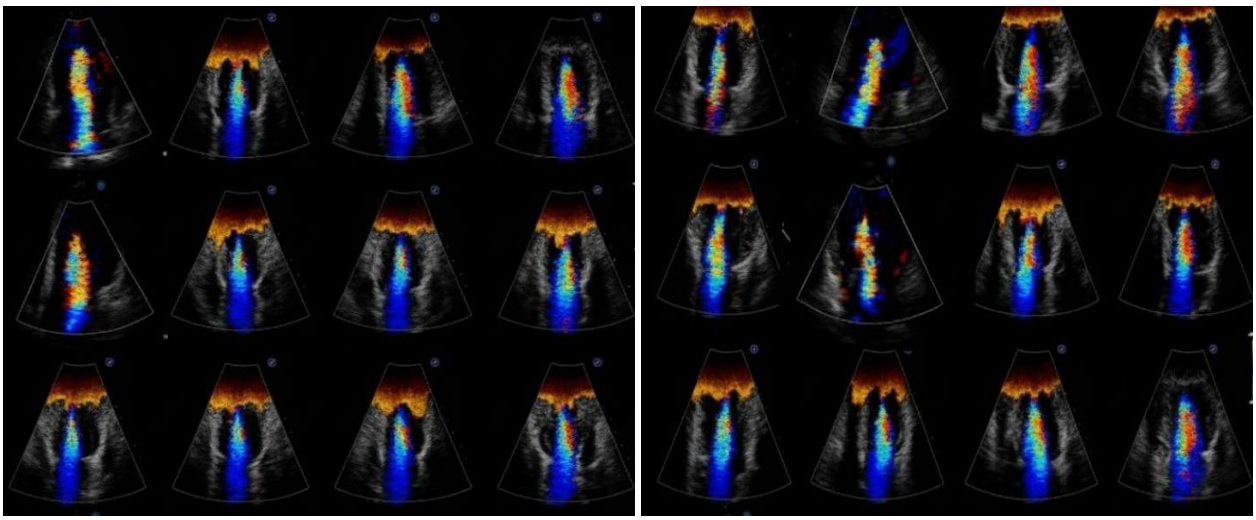
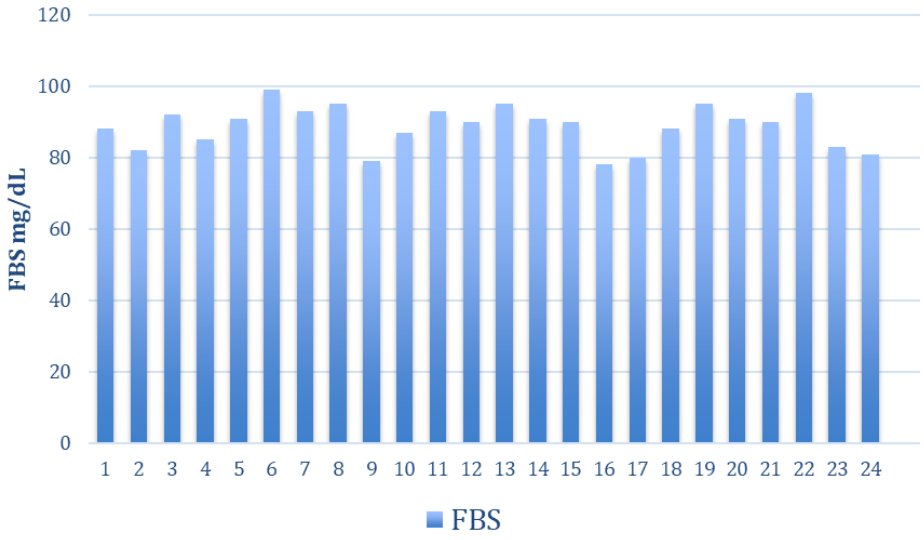
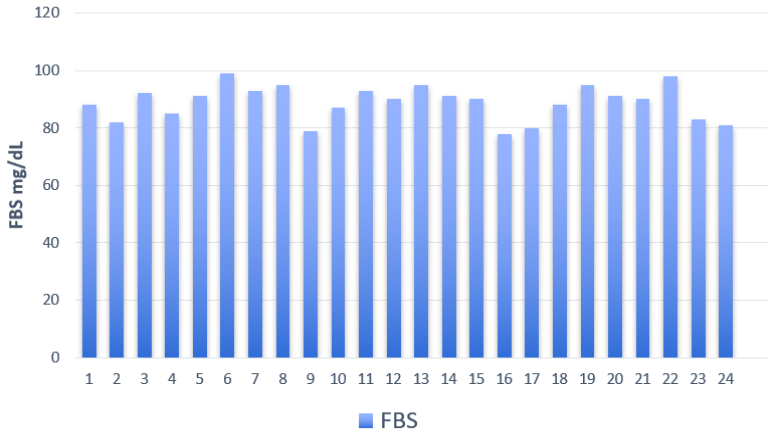


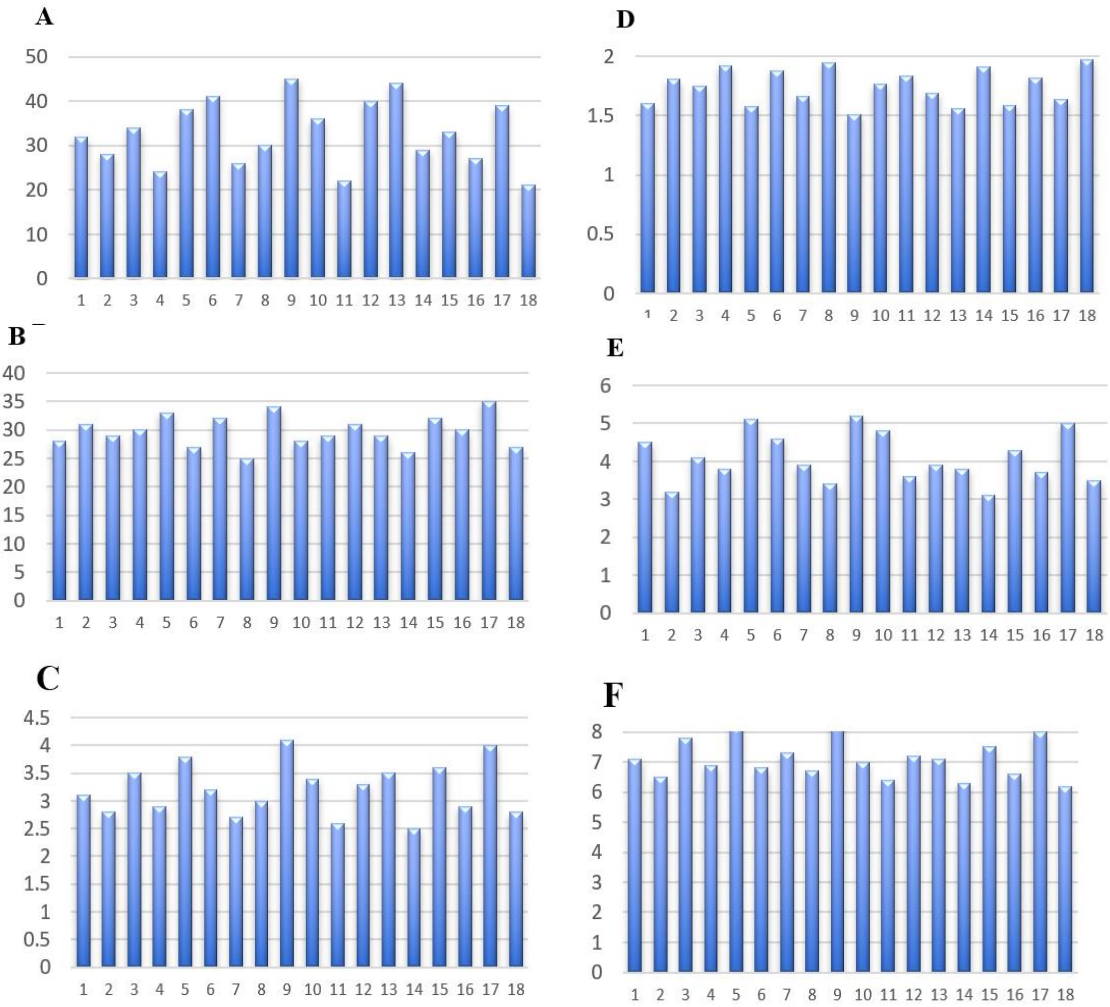
Figure 2: An example of a color Doppler echocardiography image used in the assessment of coronary flow reserve [CFR]. The flow pattern in the left ventricular outflow tract suggests the presence of microvascular dysfunction.



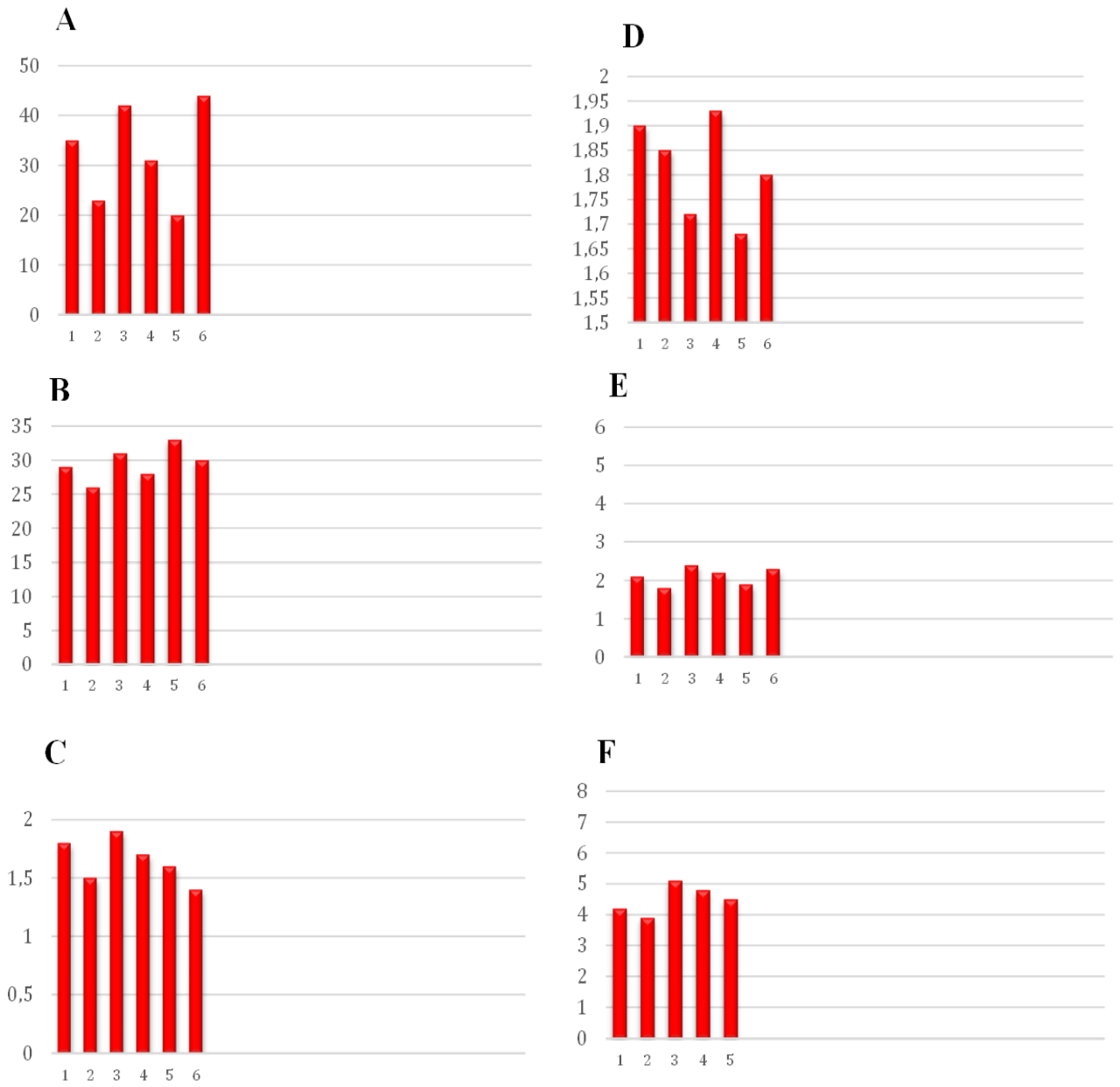
Graph-2. The amount of FBS in 24 patients.



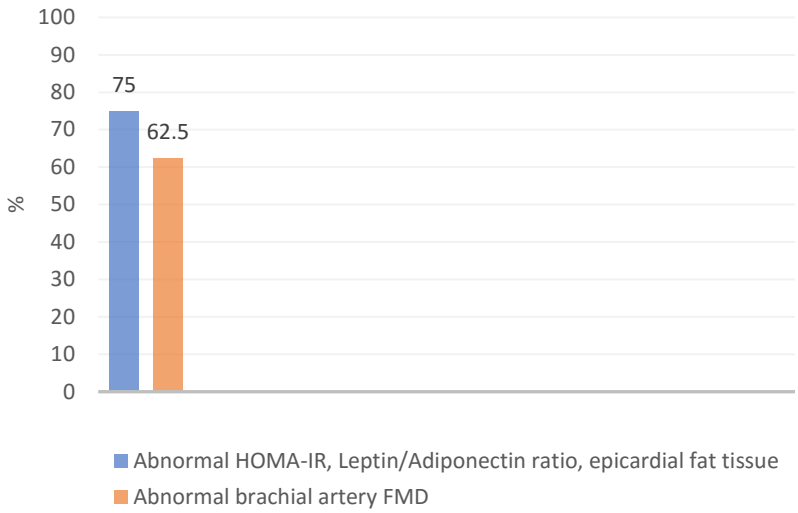
Graph-3. The 3-month HbA1c levels of 24 patients.



Graph-4. A. This graph shows the age distribution of 18 patients -B. This graph shows the BMI [Body Mass Index] distribution of 18 patients. The threshold for a normal BMI value is 25. All patients have a BMI above 25. -C. This graph shows the HOMA-IR distribution of 18 patients. The threshold for a normal HOMA-IR value is 2, and it should be below 2. All patients have a HOMA-IR above 2. -D. This graph shows the CFR [Coronary Flow Reserve] distribution of 18 patients. The threshold for a normal CFR value is 2, and it should be above 2. All patients have a CFR below 2. -E. This graph shows the distribution of the Leptin/Adiponectin ratio for 18 patients. The threshold for a normal Leptin/Adiponectin ratio is 3, and it should be below 3. All patients have a Leptin/Adiponectin ratio above 3. -F. This graph shows the epicardial fat tissue [EFT] distribution of 18 patients. The threshold for a normal epicardial fat tissue value is 6 mm, and it should be below 6 mm. The epicardial fat tissue value of the patients is above 6 mm.



Graph-5. A. This graph shows the age distribution of 6 patients. -B. This graph shows the BMI [Body Mass Index] distribution of 6 patients. The threshold for a normal BMI value is 25. All patients have a BMI above 25. -C. This graph shows the HOMA-IR distribution of 6 patients. The threshold for a normal HOMA-IR value is 2, and it should be below 2. All 6 patients have a HOMA-IR below 2. -D. This graph shows the CFR [Coronary Flow Reserve] distribution of 6 patients. The threshold for a normal CFR value is 2, and it should be above 2. All patients have a CFR below 2. -E. This graph shows the distribution of the Leptin/Adiponectin ratio for 6 patients. The threshold for a normal Leptin/Adiponectin ratio is 3, and it should be below 3. In all 6 patients, the Leptin/Adiponectin ratio is below 3. -F. This graph shows the epicardial fat tissue [EFT] distribution of 6 patients. The threshold for a normal epicardial fat tissue value is 6 mm, and it should be below 6 mm. The epicardial fat tissue value of all 6 patients is below 6 mm.



Graph-6. The distribution of abnormal HOMA-IR, Leptin/Adiponectin ratio, epicardial fat tissue, and brachial artery FMD, shown as percentages, in 24 patients with abnormal CFR and BMI.

Discussion

The findings obtained support that coronary microvascular dysfunction [CMD] is a significant problem even in young women with normoglycemic insulin resistance. The co-existence of insulin resistance in all 18 patients and the presence of endothelial dysfunction and CMD in 15 of these 18 patients suggest a close interaction between these two conditions. It is thought that insulin resistance impairs vascular dilation by disrupting endothelial nitric oxide synthase [eNOS] activity, thereby setting the stage for microvascular dysfunction [23, 24, 25, 26, 27]. Furthermore, the increased epicardial fat thickness observed in the 18 patients suggests that this fat tissue around the heart is metabolically active and may contribute to microvascular dysfunction through the release of pro-inflammatory cytokines. Adipokines secreted from epicardial fat tissue have been shown to increase local oxidative stress and trigger endothelial dysfunction in the coronary microvasculature [28, 29, 30, 31, 32]. These findings support the hypothesis that CMD may not only be a structural problem but also a cardiovascular reflection of a systemic metabolic disorder. It is suggested that each component of the metabolic syndrome has direct negative effects on microvascular structures, which independently increases the risk of cardiovascular events [33,34,35,36,37,38].

Conclusion

In 15 of the 24 patients [62.5%], CFR, BMI, brachial artery FMD, HOMA-IR, Leptin/Adiponectin ratio, and epicardial fat tissue were found to be abnormal. This study revealed a high prevalence of coronary microvascular dysfunction [CMD] in young women who presented to the hospital with dyspnea, chest pain, and hypertension, despite having normal blood sugar but insulin resistance. Our findings emphasize that the treatment of CMD should not only target cardiac symptoms but also address the underlying metabolic disorders. We suggest that CMD represents an "invisible threat" in this population and that metabolic parameters should be scrutinized more carefully during routine check-ups. Future studies should be conducted in larger patient populations to confirm these findings and evaluate the clinical outcomes of treatments targeting metabolic parameters in these patients.

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