Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/tj0npz46

HYPERINSULINEMIA AS A PREDICTING BIOMARKER OF CORONARY ARTERY DISEASE IN METABOLIC SYNDROME

Sumit Parashar[1], Dr Sandeep Tripathi[2*], Dr Mahaveer Singh[3], Dr Ashish Gupta[4], Dr Sushma BJ[5], Dr Sundeep Mishra[6], Dr Shivang Mishra[7], Dr MN Khan[8]

[1]Tutor & PhD Scholar, Dept. of Biochemistry, National Institute of Medical Sciences & Research, NIMS University, Rajasthan, Jaipur
[2*]Professor, Dept. of Biochemistry, National Institute of Medical Sciences & Research, NIMS University, Rajasthan, Jaipur
[3]Associate Professor, Dept. of Endocrinology, National Institute of Medical Sciences & Research, NIMS University, Rajasthan, Jaipur
[4]Professor & Head, Dept. of Pathology National Institute of Medical Sciences & Research, NIMS University, Rajasthan, Jaipur
[5] Professor & Head, Dept. of Biochemistry, National Institute of Medical Sciences & Research, NIMS University, Rajasthan, Jaipur
[6]Professor & Head, Dept. of Cardiology, National Institute of Medical Sciences & Research, NIMS University, Rajasthan, Jaipur
[7]Assistant Professor, Dept. of Pharmacy, Nims Institute of Pharmacy, NIMS University Rajasthan, Jaipur
[8]Professor & Head, Dept. of Biochemistry, Saraswathi Institute of Medical Sciences, Hapur, Uttar Pradesh

***Corresponding Author:** Dr Sandeep Tripathi
*Professor, Dept. of Biochemistry, National Institute of Medical Sciences & Research, NIMS University, Rajasthan, Jaipur. *Email: sandeeptripathiphd@gmail.com

ABSTRACT

Background: Insulin resistance and its metabolic consequences are increasingly being recognized as risk factors for Coronary Artery Disease (CAD). Being obese and the further accumulation of CAD risk factors related to insulin resistance, creates a state of high risk for diabetes mellitus and coronary artery diseases.

Objectives:

• To find out the prevalence of hyperinsulinemia in individuals with metabolic syndrome, both in patients with and without coronary artery disease (CAD).
• To assess the role of hyperinsulinemia as predictor of CAD risk in metabolic syndrome patients

Materials and Methods: In this comparative, cross-sectional study, 200 patients with clinically diagnosed metabolic syndrome according to the NCEP ATP III criterion were selected out of which 100 were diagnosed cases of CAD (cases) selected from the CCU of Cardiology department and 100 without CAD (controls) were selected from the OPD of Endocrinology department of our tertiary care NIMS Hospital. For estimation of fasting serum insulin & lipid profile, fasting blood sample was collected and were performed in the Central Biochemistry Laboratory, NIMS Hospital.

Results: Our study investigated the relationship between Metabolic Syndrome (MetS) and Coronary Artery Disease (CAD). We found that MetS patients with CAD were significantly older than those without CAD. Furthermore, CAD patients exhibited elevated fasting insulin levels, with a median

value of 10.42 μIU/ml (6.49-19.55), compared to 9.47 μIU/ml (6.28-13.28) in non-CAD patients. Hyperinsulinemia was also more prevalent in CAD patients, affecting 17% of this group versus 6% of non-CAD patients. Additionally, median HOMA-IR values were higher in CAD patients (2.61 [1.898-5.07]) than in non-CAD patients (2.38 [1.45-3.42]). Although LDL and TAG levels were comparable between groups, HDL levels were significantly lower in CAD patients ($p < 0.001$). Logistic regression analysis revealed that MetS with CAD patients who had high fasting insulin levels had a 3.4-fold increased risk of developing CAD compared to MetS patients without CAD.
Conclusion: Our research suggests that Hyperinsulinemia (elevated insulin levels) serves as a reliable predictive biomarker for CAD in patients with Metabolic Syndrome (MetS), making it a valuable tool for diagnostic monitoring and follow-up care, ultimately enhancing the prevention and management of CAD in this patient population

Keywords: Coronary Artery Disease (CAD), Metabolic Syndrome (MetS), Fasting Insulin, Hyperinsulinemia, HOMA-IR.

1. INTRODUCTION:

The fasting insulin levels in serum has been an important parameter of insulin sensitivity in many studies conducted epidemiologically [1,2] and hyperinsulinemia indicates insulin resistance in the body. India contributes around 15-16 % of mortality which occurs due to coronary heart disease globally [4]. Metabolic disorders related to insulin resistance are now identified as risk factors for CAD.

The main risk factors which are present in metabolic syndrome are dyslipidaemia (high triglycerides and low levels of HDL-cholesterol), hypertension, hyperglycaemia and obesity. These factors increase the overall risk of coronary artery diseases at any LDL-cholesterol level present in a patient [5,6]. Also, there is important evidence that abnormalities related to homoeostasis [3] and chronic inflammation [7,8] could be clustered together with other risk factors that are present in the metabolic syndrome.

Due to increase in being overweight and obesity globally, there is a very high increase in type 2 diabetes cases and it is expected that it will cause an increase in coronary artery diseases (CAD) as well.[9] Being obese and the further accumulation of CAD risk factors related to insulin resistance, creates a state of high risk for diabetes mellitus and coronary artery diseases. For comparing studies at global level, the WHO released an updated definition of metabolic syndrome.[10]

In this study, an attempt has been made to find out an association between hyperinsulinemia & insulin resistance with CAD in North West Indian patients, i.e. we want to find out if hyperinsulinemia is directly a risk causing factor for coronary artery disease and can be used as a predicting biomarker for CAD in MetS patients.

2. METHODS

2.1 Study design & Population

It was a comparative and cross-sectional study, and was conducted in the Department of Biochemistry in association with Department of Cardiology & Department of Endocrinology, National Institute of Medical Sciences and Research, Jaipur, Rajasthan. This study was conducted between the period July 2023 to September 2024, which included metabolic syndrome patients with CAD (cases) & metabolic syndrome patients without CAD (controls). The inclusion criterion for cases was (a) age 18-75 years, (b) diagnosed cases of metabolic syndrome according to the NCEP ATP III criterion [11], (c) confirmed diagnosed cases of CAD (d) willingness to participate in the study with informed consent. The inclusion criterion for controls was (a) age 18-75 years (b) Diagnosed cases of metabolic syndrome based on the NCEP ATP III criterion (c) No history or diagnosis of CAD (d) Willingness to participate in the study with informed consent. The patients who did not meet the criterion for cases and controls and those patients suffering from acute or chronic diseases like liver disease, renal disease, respiratory and immunodeficiency diseases, Patients having UTI, Thyroid disorders and

psychiatric illness, Subjects on insulin therapy or having Type I diabetes mellitus or Active malignancies, Subjects with Pregnancy were excluded from the study.

2.2 Study Recruitment

In our study, we included 200 subjects which clinically diagnosed cases of Metabolic Syndrome based on the modified NCEP ATP III criterion. Out of these 200 subjects, 100 were confirmed diagnosed patients of coronary artery disease (cases-MetS with CAD), selected from the CCU of cardiology department of NIMS hospital, and 100 were subjects having metabolic syndrome without CAD (controls-MetS without CAD), selected from the OPD of endocrinology department. Data of all patients, including demographic, anthropometric & biochemistry laboratory parameters were taken and performed after taking the informed consent of the subjects.

2.3 Collection of clinical data and parameters

Metabolic syndrome subjects were selected through the NCEP ATP III criterion [9]. CAD patients were confirmed cases diagnosed by angiography admitted in the CCU. For estimation of biochemical parameters (lipid profile, FBS, HbA1c) fasting blood sample of the patients was collected and the tests were performed in the Central Biochemistry Laboratory, NIMS Hospital, Jaipur. For estimation of fasting serum insulin, fasting blood sample was collected and estimated on VITROS 5600 in the Central Biochemistry Laboratory, NIMS hospital, Jaipur.
Other data like demographic and anthropometric data was taken from patient case record files from the CCU & OPD of Cardiology & Endocrinology.

2.4 Biochemistry Laboratory Investigations

Serum lipid profile (Total Cholesterol, LDL, HDL, TAG, VLDL) was estimated on VITROS 5600 Integrated system. Total cholesterol (<200 mg/dl) was estimated by enzymatic colorimetric method. LDL (<100 mg/dl) was estimated enzymatic endpoint method. HDL (>60 mg/dl) was estimated by precipitation colorimetric method. TAG was estimated by enzymatic colorimetric method.
Fasting blood glucose (70-100 mg/dl) was estimated by enzymatic colorimetric method on VITROS 5600 Integrated System. Serum Fasting Insulin (2.3-26 μIU/ml) was estimated on VITROS 5600 Integrated System by immunometric immunoassay technique.

2.5 Ethics

Our present study was done with the approval of the Institutional Review Board (approval number: NIMSUR/IEC/2022/372). Informed consent of all the patients was taken before their participation in this comparative, cross-sectional study.

2.6 Statistical Analysis

The statistical analysis of the data was done on IBM SPSS software and MS Excel. Normality was checked by Kolmogorov-Smirnov test for all variables. Parametric data i.e. continuous variables were expressed as mean and standard deviation, and T-test was used to compare their mean. The non-parametric data was expressed as median and Mann-Whitney U test was used for comparing their median. The categorical data was expressed as frequency distribution Logistic regression analysis was used for assessing the association between the main variable of the study & CAD, Fasting Insulin. Level of significance was set at 5% (i.e. if p value <0.05, then it was considered statistically significant).

3. RESULTS:

Table 1. Demographic and Anthropometric Details

Variables	Metabolic Syndrome with CAD	Metabolic Syndrome without CAD
Subjects	100	100
Age, Years Mean ± SD	58.42 ± 1.12	49.90 ± 1.11
Gender, n (%)		
Male	76 (76%)	65 (65%)
Female	24 (24%)	35 (35%)
BMI, Median[Q1-Q3]	25.32 [23.92 – 27.26]	26.41 [24.57 – 28.49]
Systolic Blood Pressure	134.56 ± 15.27	135.5 ± 9.21
Diastolic Blood Pressure	86.33 ± 11.34	87.28 ± 5.95
The data is presented in Mean ± SD, number (percentage) and Median [Q1-Q3].		

Table 1 shows the average age of the subjects with CAD was found to be significantly higher, with a mean age of 58.42 ± 1.12 years, compared to 49.90 ± 1.11 years in the group without CAD. Gender distribution also showed a higher proportion of males in both groups, with 76% (n=76) in the CAD group and 65% (n=65) in the non-CAD group, while females comprised 24% (n=24) and 35% (n=35), respectively. Regarding Body Mass Index (BMI), the median [Q1-Q3] values revealed a slightly lower BMI in the CAD group at 25.32 [23.92 – 27.26] compared to 26.41 [24.57 – 28.49] in the non-CAD group. The data suggest that older age and male gender may be associated with an increased risk of CAD in patients with metabolic syndrome, with differences in BMI also noted between the groups.

Table 2: Comparing mean/median of lipid profile parameters of patients in MetS with & without CAD by using t-test & Mann-Whitney U test

Variables	MetS with CAD	MetS without CAD	P - Value
T. Cholesterol (mg/dl)	160.28 ± 42.11	188.3 ± 27.06	< 0.001
HDL (mg/dl)	36.62 ± 9.71	40.98 ± 7.34	< 0.001
LDL (mg/dl)	104.61 ± 35.35	112.1 ± 24.74	0.08402
VLDL (mg/dl)	32.4 (25.5-40.1)	33 (31.15-37)	0.1443**
TAG (mg/dl)	162 (127.5-200.3)	165 (155.8-185)	0.1443**

****: Mann-Whitney U test used**

Table 2 shows the mean/median values of lipid profile parameters in both cases and controls.
The mean of total cholesterol levels in cases and controls were 160.28±42.11 and 188.3±27.06, respectively, which shows that controls had higher mean value than cases and the difference was statistically highly significant ($p<0.001$). The mean of HDL levels was lower in cases as compared to controls and the difference was statistically highly significant ($p<0.001$). The difference in mean values of LDL was statistically not significant, the difference in median values of TAG & VLDL in both the groups, was statistically not significant ($p>0.05$) (Table 2).

Table 3: Frequency distribution of fasting insulin of patients of both groups

Insulin	MetS with CAD		MetS without CAD	
	n = 100	**In %**	**n = 100**	**In %**
< 2.3 µIU/ml	5	5%	0	0%
2.3 - 26 µIU/ml	78	78%	94	94%
> 26 µIU/ml	17	17%	6	6%

Table 3 shows the frequency distribution of fasting insulin in cases and controls.
Hyperinsulinemia (Fasting insulin >26 µIU/ml) was present in 17(17%) patients in cases and 6(6%) in controls.

Graph 1:

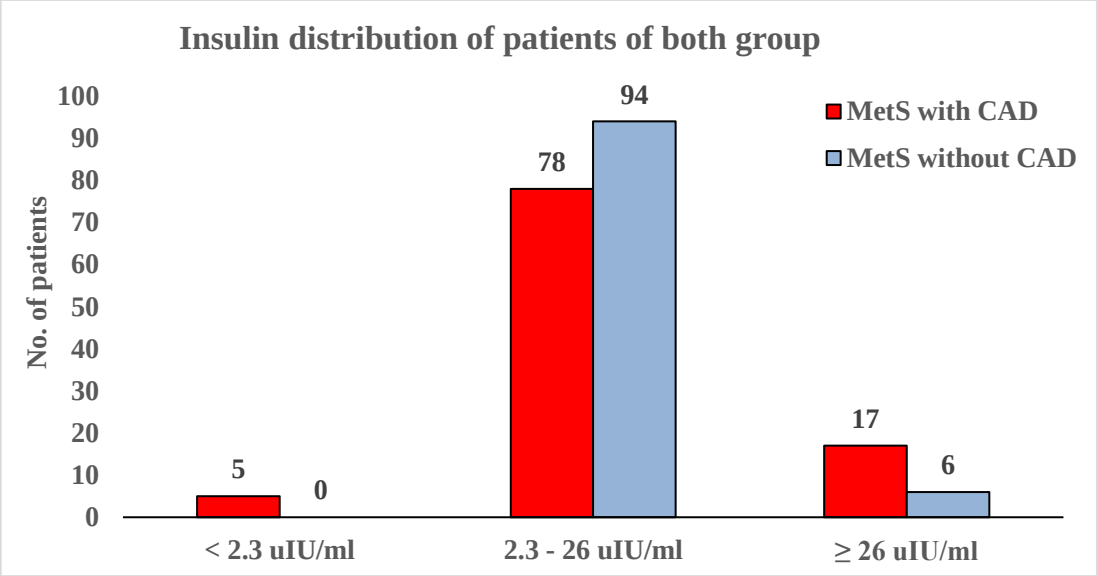

Table 4: Comparing mean/median of Insulin, HbA1c, Fasting Glucose & HOMA-IR of patients between MetS with & without CAD by using Mann-Whitney U test & t-test

Variables	MetS with CAD	MetS without CAD	P - Value	Significance
INSULIN	10.42 (6.49-19.55)	9.47 (6.28-13.28)	0.10524**	Not Significant
HBA1C	6.93 ± 1.62	7.65 ± 1.46	0.00113	Significant
Fasting Glucose	109.15 ± 14.54	102.26 ± 14.98	0.00114	
HOMA-IR	2.61 (1.898-5.07)	2.38 (1.45-3.42)	0.0357**	Not Significant

****: Mann-Whitney U test used**

Table 4 shows the mean/median values of Fasting Insulin, HbA1c, Fasting Glucose & HOMA-IR of both cases & controls.
The median insulin levels were higher in cases [10.42 (6.49-19.55)] as compared to controls [9.47 (6.28-13.28)], the difference was statistically not significant (p>0.05). The median of calculated parameter for insulin resistance, HOMA-IR was higher in cases [2.61 (1.898-5.07)] as compared to controls [2.38 (1.45-3.42)], the difference was statistically not significant (p>0.05). The mean levels of fasting glucose were higher in cases (109.15 ± 14.54) as compared to controls (102.26 ± 14.98), the difference was statistically significant(p<0.05). The mean levels of HbA1c were lower in cases (6.93 ± 1.62) as compared to controls (7.65 ± 1.46), the difference was statistically significant(p<0.05).

Table 5: Logistic regression of Fasting Insulin in MetS with CAD compared to MetS without CAD

Variables		MetS with CAD	MetS without CAD	Odd's Ratio	95% Confidence Interval	Z-test	P - Value
Insulin	**< 2.3 µIU/ml**	**5**	**0**	**-**	**-**	**-**	**-**
	2.3 - 26 µIU/ml	**78**	**94**	**1**	**-**	**-**	**-**
	> 26 µIU/ml	**17**	**6**	**3.415**	**1.284 - 9.08**	**2.461**	**0.0138**

Table 5 shows the logistic regression analysis of Fasting Insulin in both groups, cases and controls. In MetS with CAD group 17(17%) patients have high fasting insulin levels (>26 μIU/ml) and in MetS without CAD 6(6%) patients have high fasting insulin levels (>26 μIU/ml). According to the regression analysis for Fasting Insulin between cases and controls, the odd's ratio is 3.41, which is statistically significant($p<0.05$), which means that MetS with CAD group with high Fasting Insulin has 3.4 times risk of developing CAD than MetS without CAD with high Fasting Insulin.

4. DISCUSSION:

Our study investigated the relationship between Metabolic Syndrome (MetS) and Coronary Artery Disease (CAD). We found a significant age disparity between MetS patients with CAD (58.42 ± 1.12 years) and those without CAD (49.90 ± 1.11 years; $p < 0.001$), indicating CAD is more prevalent in older adults. Males dominated both groups, comprising 76% of CAD patients and 65% of non-CAD patients, suggesting males are at higher risk for MetS and CAD.

Body Mass Index (BMI) analysis revealed a slightly lower median BMI in CAD patients (26.41 [24.57-28.49]) compared to non-CAD patients (25.32 [23.9-27.26]), with most patients in both groups being overweight or obese.

Lipid profile analysis showed comparable mean LDL levels between CAD (104.61 ± 35.35 mg/dl) and non-CAD (112.1 ± 24.74 mg/dl) patients [12, 13]. Median TAG levels were slightly higher in non-CAD patients (165 [155.8-185] mg/dl) versus CAD patients (162 [127.5-200.3] mg/dl), but the difference was statistically insignificant ($p > 0.05$) [18, 19]. Lower LDL and TAG levels in CAD patients may be attributed to treatment with statins and aspirin for dyslipidemia and chronic heart disease [15], particularly given the older age and previous hospitalizations in this group.

Notably, mean HDL levels were significantly lower in CAD patients (36.62 ± 9.71 mg/dl) compared to non-CAD patients (40.98 ± 7.34 mg/dl; $p < 0.001$) [13, 19]. This disparity suggests impaired reverse cholesterol transport mechanisms, increasing CAD risk [18, 20]. Lower HDL levels in older adults may also result from decreased protein intake and negative nitrogen balance, affecting lipoprotein synthesis [14).

Fasting insulin levels were similar between CAD (10.42 [6.49-19.55] μIU/ml) and non-CAD (9.47 [6.28-13.28] μIU/ml) patients. However, the prevalence of hyperinsulinemia (> 26 μIU/ml) was higher in CAD patients (17%) versus non-CAD patients (6%) [16, 17]. Median HOMA-IR values indicated higher insulin resistance in CAD patients, although the difference was statistically insignificant ($p > 0.05$).

Logistic regression analysis revealed a 3.4-fold increased risk of developing CAD in MetS patients with high fasting insulin levels ($p < 0.001$) [17]. Our findings underscore the importance of considering HDL levels and insulin resistance as key risk factors for CAD in MetS patients, particularly in older adults.

Our results and analysis of Fasting Insulin among cases and controls showed that prevalence of hyperinsulinemia was higher in cases than controls and also, the median fasting insulin levels were higher in cases than controls.

5. CONCLUSION:

The findings of our study showed that MetS with CAD patients have higher Fasting Insulin levels (hyperinsulinemia), higher HOMA-IR & higher prevalence of hyperinsulinemia in cases as compared to controls and significantly lower HDL levels in cases as compared to controls, indicating that low HDL levels and high Fasting Insulin levels are a high-risk factor for MetS with CAD patients as compared to MetS without CAD. So, it is highly important to maintain the HDL levels in CAD and MetS patients, also protein diet should be maintained properly, and most importantly Fasting Insulin levels can be used as a predicting biomarker for CAD in MetS patients. Our research indicates that Hyperinsulinemia is a significant marker for identifying CAD risk in MetS patients, which will help in better management of CAD.

Conflict of Interest
Nil

6. Funding

This present research study was carried out with the help of NIMS University, Rajasthan, Jaipur. There was no additional support or funding from any other public, private or non-profit organizations.

7. REFERENCES:

[1] Deckert T, Feldt-Rasmussen B, Borch-Johnsen K, Jensen T, Kofoed-Enevoldsen A. Albuminuria reflects widespread vascular damage. Diabetologia. 2009; 32 : 219-26.
[2] Zandbergen AA, Vogt L, De Zeeuw D, Lamberts SW, Ouwendijk RJ, Baggen MG, Bootsma AH. Change in albuminuria is predictive of cardiovascular outcome in normotensive patients with type 2 diabetes and microalbuminuria. Diabetes Care. 2007; 30 : 3119-21.
[3] Zavaroni I, Bonora E, Pagliara M, Dall'Aglio E, Luchetti L, Buonanno G, Bonati PA, Bergonzani M, Gnudi L, Passeri M, Reaven G. Risk factors for coronary artery disease in healthy persons with hyperinsulinemia and normal glucose tolerance. New England journal of medicine. 2009; 320 : 702-6.
[4] Haffner SM, Valdez RA, Hazuda HP, Mitchell BD, Morales PA, Stern MP. Prospective analysis of the insulin-resistance syndrome (syndrome X). Diabetes. 2012;41:715-22.
[5] Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation and treatment of high blood cholesterol in adults (Adult Treatment Panel III). JAMA 2011;285:2486 – 97.
[6] Third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation and treatment of high blood cholesterol in adults (Adult Treatment Panel III) Final report. National Heart, Lung and Blood Institute. National Institutes of Health 2012; NIH Publication 01-3670.
[7] Juhan-Vague I, Thompson SG, Jespersen J. Involvement of the hemostatic system in the insulin resistance syndrome. A study of 1500 patients with angina pectoris. The ECAT Angina Pectoris Study Group. Arterioscler Thromb 2013;13:1865 – 73.
[8] Festa A, D'Agostino Jr R, Howard G, Mykkanen L, Tracy RP, Haffner SM. Chronic subclinical inflammation as part of the insulin resistance syndrome: the Insulin Resistance Atherosclerosis Study (IRAS). Circulation 2009;102:42 – 7.
[9] Mokdad AH, Ford ES, Bowman BA, Dietz WH, Vinicor F, Bales VS, Marks JS. Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001. JAMA. 2008;289:76 –79.
[10] World Health Organization: Definition, Diagnosis and Classification of Diabetes Mellitus: Report of a WHO Consultation. Part 1: Diagnosis and Classification of Diabetes Mellitus. Geneva, Switzerland: World Health Organization; 2009. WHO/NCD/NCS/99.2.
[11] Huang PL. A comprehensive definition for metabolic syndrome. Dis Model Mech. 2009 May-Jun;2(5-6):231-7. doi: 10.1242/dmm.001180. PMID: 19407331; PMCID: PMC2675814.
[12] Prashant Udgire & N D Karnik: Lipid Profile in Metabolic Syndrome Patients : A Indian Perspective. International Journal of current Medical and Applied sciences; 2017, 13(3), 168-173
[13] Montazerifar, F., Bolouri, A., Mahmoudi Mozaffar, M., & Karajibani, M. (2016). The Prevalence of Metabolic Syndrome in Coronary Artery Disease Patients. *Cardiology Research, 7*(6), 202-208.
[14] Stefan M Pasiakos, Harris R Lieberman, Victor L Fulgoni, Higher-Protein Diets Are Associated with Higher HDL Cholesterol and Lower BMI and Waist Circumference in US Adults, The Journal of Nutrition, Volume 145, Issue 3, 2015, 605-614, ISSN 0022-3166, https://doi.org/10.3945/jn.114.205203.
[15] Chow, Benjamin J.W. et al Prognostic and Therapeutic Implications of Statin and Aspirin Therapy in Individuals with Nonobstructive Coronary Artery Disease Vol. 35: 4, 2015: 981-989 doi: 10.1161/ATVBAHA.114.304351

[16] Metwally, Y.G., Sedrak, H.K. & Shaltout, I.F. The relationship between coronary artery severity and insulin resistance in patients with impaired glucose tolerance and metabolic syndrome. *Egypt J Intern Med* **32**, 21 (2020). https://doi.org/10.1186/s43162-020-00022-z

[17] Fazio S, Mercurio V, Tibullo L, Fazio V, Affuso F. Insulin resistance/hyperinsulinemia: an important cardiovascular risk factor that has long been underestimated. Front Cardiovasc Med. 2024 Mar 13;11:1380506. doi: 10.3389/fcvm.2024.1380506. PMID: 38545338; PMCID: PMC10965550.

[18] Linton MRF, Yancey PG, Davies SS, et al. The Role of Lipids and Lipoproteins in Atherosclerosis. [Updated 2019 Jan 3]. In: Feingold KR, Anawalt B, Blackman MR, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000- https://www.ncbi.nlm.nih.gov/books/NBK343489/

[19] Wilson, Peter W.F., D'Agostino, Ralph B., Parise, Helen, Sullivan, Lisa. Metabolic Syndrome as a Precursor of Cardiovascular Disease and Type 2 Diabetes Mellitus. 2005: 112(20), 3066-3072

[20] Toth, Peter P. High-Density Lipoprotein and Cardiovascular Risk. 2004: 109(15), 1809-1812. doi: 10.1161/01.CIR.0000126889.97626.B8. American Heart Association