Pharmacogn J. 2024; 16(1): 195-201
A Multifaceted Journal in the field of Natural Products and Pharmacognosy
www.phcogj.com

Research Article

Evaluation of Tumor Necrosis Factor Alpha, Insulin, glucose, HbA1c% and HOMA-IR as Predictors for Cardiovascular Diseases in Patients with Type 2 Diabetes

Haider Nasser Jabber[1,2,*], Bassem Charfeddine[2], Hamed Jaddoa Abbas[3]

Haider Nasser Jabber[1,2,*], Bassem Charfeddine[2], Hamed Jaddoa Abbas[3]

[1]*College of Pharmacy, Basra University, Basrah, IRAQ.*

[2]*Department of Biochemistry, Faculty of Medicine, University of Sousse, TUNISIA.*

[3]*Al-Fayhaa Teaching Hospital – Al- Zahraa Medical college- Basrah University, Basrah, IRAQ.*

Correspondence

Haider Nasser Jabber

College of Pharmacy, Basra University, Basrah, IRAQ; Department of Biochemistry, Faculty of Medicine, University of Sousse, TUNISIA.

E-mail: haider.jabar@uobasrah.edu.iq

History

- Submission Date: 11-12-2023;
- Review completed: 10-01-2024;
- Accepted Date: 17-01-2024.

DOI : 10.5530/pj.2024.16.27

Article Available online

http://www.phcogj.com/v16/i1

ABSTRACT

Objective: Comparison of the blood level of TNFα in patients with and without type 2 diabetes who have cardiovascular diseases. Examine the connection between the amount of serum TNFα and insulin resistance in patients with type 2 diabetes who have cardiovascular diseases. **Method**: The present study included 60 patients with Diabetes Mellitus (DM) with a mean age of 56.02±1.395 years and an age range of (40 - 80)years and 60 patients with cardiovascular diseases and diabetes (CVD and DM) with a mean age of 59.20±1.478 and an age range of (40-80) years, Who visited Al-Basrah Teaching Hospital in Basrah. in addition, the study included 60 healthy controls mean age of healthy control subjects was 54.72±1.405years. All patients in this study were diagnosed by specialized doctors and the diagnosis was verified by clinical and laboratory tests, during the period from September 2022 to September 2023. All Subjects signed a written informed consent form. The BMI was calculated as body weight (kg) and was divided by squared height in meters. **Results**: The results of this study showed an increase in the level of glucose, haemoglobin A1c%, insulin, and HOMA IR (in CVD and DM patients as compared with DM patients and control and there was a significant difference in concentrations among study groups (p-value <0.0001). Also, The results of this study showed an increase in the level of tumor necrosis factor-alpha in CVD and DM patients as compared with DM and control and there was a significant difference in concentrations of TNFα among study groups (p-value <0.0001). **Conclusion**: Based on the findings of this research, it can be inferred that TNFα and HbA1c have the potential to serve as practical and straightforward indicators for predicting the coexistence of insulin resistance, dysglycemia, and Cardiovascular Diseases in seemingly healthy individuals within the young (<50 years) Al-Basra community.

Keywords: TNFα, Insulin, HOMA-IR, Cardiovascular Disease, Diabetes Mellitus and Inflammation.

INTRODUCTION

Cardiovascular diseases (CVDs), which are responsible for the highest death rates globally, result in the loss of about 17.9 million lives each year. The phrase CVDs encompasses a range of medical conditions that impact the heart and blood vessels, including maladies such as rheumatic heart disease, coronary heart disease, and cerebrovascular disease. This condition is often linked to the accumulation of lipid deposits inside the arterial walls, known as atherosclerosis, which subsequently elevates the likelihood of thrombus formation.[1]

Individuals diagnosed with type 2 diabetes mellitus (T2DM) have a heightened susceptibility to CVD that is about two to three times greater when compared to the risk seen in the general population. Based on a study conducted by researchers,[2] it was shown that a substantial proportion, namely 66.67%, of individuals diagnosed with T2DM also exhibit risk factors associated with CVD. This coexistence of illnesses poses a considerable burden on public health due to its extensive clinical and socioeconomic implications. Several factors have been identified as increasing the susceptibility to cardiovascular disease in people with T2DM. These factors include obesity, hypertension, hyperglycemia, proteinuria, a sedentary lifestyle, and dyslipidemia.[3]

Individuals diagnosed with pre-diabetes and type 2 diabetes often demonstrate the presence of insulin resistance, a physiological aberration affecting the utilisation of glucose inside their bodies. It often occurs in groups with high blood pressure, central obesity, raised total triglyceride levels, low HDL cholesterol levels, and hemostatic problems. Both those without type 2 diabetes and those who have the disease exhibit this clustering of CVD risk variables, which is a predictor of coronary heart disease (CHD).[4,5] It has been questioned whether hyperinsulinemia in and of itself is a predictor of CVD.[6] A meta-analysis of published research by Ruige *et al.* revealed a marginally favourable correlation between CVD occurrences and high insulin levels.[7]

Since it is tightly linked to a number of other risk variables, standard statistical approaches sometimes overestimate the real relevance of insulin resistance in raising the probability of CVD events. As a result, a complete model with a wide range of intercorrelated variables has been created using factor analysis. Our research revealed that the "hyperinsulinemia cluster" was linked to a higher risk of CHD mortality in those with type 2 diabetes who were middle-aged or older. This cluster exhibited a high predictive value for CHD mortality and was described by increased BMI, triglycerides, and insulin levels together with decreased HDL cholesterol levels.[8,9]

Cite this article: Jabber HN, Charfeddine B, Abbas HJ. Evaluation of Tumor Necrosis Factor Alpha, Insulin, glucose, HbA1c% and HOMA-IR as Predictors for Cardiovascular Diseases in Patients with Type 2 Diabetes. Pharmacogn J. 2024;16(1): 195-201.

In a recent research the Archimedes model was used to calculate the percentage of MIs that would be avoided if insulin resistance and other risk variables were kept at healthy levels.[10] A simulated population that is typical of young adults in the United States was created using person-specific data from the National Health and Nutrition Examination Survey 1998–2004. Preventing insulin resistance in young people would stop 42% of MIs. Systolic blood pressure (36%), HDL cholesterol (31%), LDL cholesterol (16%), fasting plasma glucose (9%), and smoking (9%) were all less significant predictors of MI than insulin resistance.

Numerous sizable prospective studies have examined the impact of hyperinsulinemia on the development of cardiovascular disease (CVD), but no clear correlation has been found yet.[11] It is well recognized that type II diabetes develops from hyperinsulinemia, which also has a poor cardiovascular risk profile. Although the risk for CVD is much higher in those with type II diabetes, it is unclear what role hyperinsulinemia plays in this process.[12] According to recent articles, hyperinsulinemia is a compensatory strategy for impaired peripheral tissue insulin sensitivity. This "insulin resistance" may be crucial in the aetiology of type II diabetes and cardiovascular disease.[6]

One of the strongest pro-inflammatory cytokines is tumor necrosis factor (TNFα), hence it was chosen as the initial target in the cytokine-targeted strategy. TNFα inhibitors are being utilized in medicine as anti-inflammatory medications, mostly to treat patients with systemic inflammatory disorders. This kind of therapy is given to almost a million patients, and TNFα antagonists are presently the most lucrative pharmacological class in the world, with annual sales of 25 billion US dollars.[13] Clinical evidence suggested that TNFα inhibitors were ineffective in treating heart failure and could perhaps make the condition worse. The causes of these underwhelming outcomes, meanwhile, are yet unclear. TNFα encourages the inflammatory response, which exacerbates the clinical issues associated with autoimmune illnesses and cardiovascular diseases, both of which have a significant link to cardiovascular comorbidity.[14]

Numerous metabolic problems, such as increased polyol flux, accumulation of advanced glycation end products, oxidative stress, and lipid changes, may be responsible for the dysregulation of TNFα control in diabetic individuals with persistent hyperglycemia.[15] TNFαcauses endothelial dysfunction, stenosis, hemodynamic irregularities, decreased perfusion, and neurotrophic impairment of blood vessels by inducing the overexpression of a number of growth factors and cell adhesion molecules within the blood vessels, additionally, it lessens the degree of vasodilation caused by nitric oxide synthase (NOS) by inhibiting the synthesis of NOS in vascular endothelial cells,[16] moreover, it stimulates the proinflammatory activity at subcellular levels.[17,18]

MATERIALS AND METHODS

The Ethical Considerations: The research included the collecting of blood samples and the implementation of experimental methods, both of which received approval from the Ethical Committee of AL Basra Teaching Hospital in Iraq and Sousse University in Tunisia. Prior to sample collection, informed permission was acquired from all subjects included in the research. Furthermore, all methodologies and procedures were conducted in accordance with the standards and regulations set out by the Ethical Committee of the Faculty of Medicine Ibn Al Jazzar, Sousse, affiliated with Sousse University in Tunisia.

Study Design: This study is a case-control study which had been performed on patients who attended Al-Basrah Teaching Hospital.

The Subjects: The present study included 60 patients with Diabetes Mellitus (DM) with a mean age of 56.02±1.395 years and an age range of (40-80)years and 60 patients with cardiovascular diseases and diabetes (CVD and DM) with a mean age of 59.20±1.478and an age range of (40-80) years, Who visited Al-Basrah Teaching Hospital in Basrah. in addition, the study included 60 healthy controls mean age of healthy control subjects was 54.72±1.405 years. All patients in this study were diagnosed by specialized doctors and the diagnosis was verified by clinical and laboratory tests, during the period from September 2022 to September 2023. All Subjects signed a written informed consent form. The BMI was calculated as body weight (kg) and was divided by squared height in meters.

The Collection of the Samples: Five millilitres of each patient's and control's blood sample is taken. The serum was then removed from the samples and kept at -20 degrees Celsius until analysis. The samples were then placed into anticoagulant tubes containing sodium citrate, centrifuged for 15 minutes at 3000 rpm, and then centrifuged again. The remaining samples are put into sterile test tubes and allowed to coagulate at room temperature for 30 minutes. After 15 minutes of centrifugation at 3000 rpm to separate the sample, the serum was collected and kept at -20°C for further analysis.

The Biochemical Analysis: serum were analysed for glucose measurement (colorimetric method) using kit supplied by Biosystem (spain), HbA1c by standardized direct methods using kit supplied by Biosystem (Spain), TNFα and insulin using ELISA technique by kits supplied by Elabscience (USA)

RESULTS

Age and sex were matched between the studied group with no significant ($p>0.05$) differences exists between the groups, while there was a significant difference in mean BMI among study groups (p-value <0.0001) (Table 1).

The results of this study showed an increase in the level of glucose (301.6±9.620) (mg/dL) in CVD and DM patients as compared with DM patients and control, (227.0±6.053), (97.68±1.014), (mg/dL) respectively, and there was a significant difference in concentrations glucose among study groups (p-value <0.0001). The results of this study showed an increase in the level of hemoglobin A1c% (12.08±0.2337) % in CVD and DM patients as compared with DM patients and control, (9.165±0.2329), 4.917±0.06139), %respectively and there was a significant difference in concentrations of HbA1c among study groups (p-value <0.0001). The results of this study showed an increase in the level of insulin mIU/ml (26.49±0.5756) (mIU/ml) in CVD and DM patients as compared with DM patients and control, (20.40±0.6199), (7.314±0.2871), (mIU/ml) respectively, and there was a significant difference in concentrations of insulin among study groups (p-value <0.0001). The results of this study showed an increase in the level of homeostatic model assessment for insulin resistance (HOMA IR) (19.74±0.7800) in CVD and DM patients as compared with DM patients and control, (11.61±0.5459), (1.768±0.07192), respectively and there was a significant difference in concentrations of HOMA IR among study groups (p-value <0.0001). The results of this study showed an increase in the level of tumor necrosis factor alpha (TNFα)(132.4±3.918) (pg/mL) in CVD and DM patients as compared with DM and control, (119.5±5.091), (36.42±1.448), (pg/mL) respectively, and there was a significant difference in concentrations of TNFα among study groups (p-value <0.0001) (Table 2).

DISCUSSION

One of the leading causes of mortality in the majority of industrialised nations is cardiovascular disease (CVD), which is mostly brought on by coronary artery atherosclerosis. Age, gender, economic status, and other factors all affect CVD incidence. Highly correlated processes seen in atherosclerosis include lipid abnormalities, thrombosis, inflammation, activation of vascular smooth cells and platelets, endothelial dysfunction, oxidative stress, and hereditary variables.[19,20] The mean

age of control subjects was 54.72±1.405 years, that of diabetes mellitus groups was 56.02±1.395 years and cardiovascular disease and diabetes groups was 59.20±1.478years mellitus and there was no significant difference in mean age among study groups; this result agrees with(21), who found that the mean age of patients with CVD was(55) years. Also, the results came in agreement with a previous study who observed that the mean age of patients with CVD was 64.72 years (55.6-73.8 years).[22]

The findings of our investigation concurred with a previous study, which discovered that the elderly and ageing populations are more vulnerable to CVD.[23] High age-related CVD incidence is associated with a number of wider ageing processes, including morbidity accumulation, a decline in homeostasis, and persistently harmful effects of CVD risk factors. Insidious aging-related alterations in CVD morphology and function are another cause of heart disease.[24] For instance, vascular stiffening of the central vasculature is a constant ageing phenomenon that typically begins by middle age and progresses to increased afterload stress, increased myocardial workload, and changes in diastolic perfusion that predispose to functional declines and ultimately lead to ischemia, heart failure, arrhythmia, and other CVD disorders.[25]

Moreover, the senior demographic has a higher susceptibility to sarcopenic obesity and heightened insulin resistance compared to middle-aged individuals, mostly as a result of advancing age, hormonal fluctuations, and a predominantly inactive way of life. Consequently, this population faces an elevated likelihood of developing diabetes.[26] The process of ageing is associated with an increase in blood triglyceride (TG) levels and alterations in the metabolism of triglycerides inside the body. The aforementioned circumstances have been seen to increase the susceptibility of older individuals to the development of metabolic-related disorders, such as diabetes and metabolic syndrome, in comparison to younger individuals.[27,28] Although there is a general rise in cardiovascular disease (CVD) with advancing age, cardiologists encounter the task of customising preventative and treatment strategies based on the unique circumstances of each person.[29] The outcomes of our study have disagreed with,[30] which did not contribute to explaining the higher prevalence and extent of CVD observed in elderly patients.

The current research found that, in terms of body mass index (BMI), patients with CVD and DM had mean BMIs that are considerably higher than those of the DM and controls. These findings support[31] they noted that the average BMI of CVD patients was below 25, and they proposed that obesity is a separate risk factor for CVD in both sexes. The results also support,[32] they discovered that a greater risk profile and BMI are both strongly connected with an increased risk of cardiovascular risk factors.[33] It has been found that individuals with a higher BMI have a greater likelihood of being linked to cardiovascular risk factors such as hypertension, hypercholesterolemia, and diabetes mellitus.

The condition of obesity has been shown to be correlated with a heightened likelihood of developing cardiovascular disease, and there is a possibility of a stronger manifestation of CVD in individuals with obesity. Inflammatory responses have been observed in individuals with obesity, resulting in elevated levels of clotting factors such as fibrinogen, von Willebrand factor, and factors VII and VIII. Additionally, there is an increase in plasminogen activator inhibitor type-I, which is associated with reduced fibrinolysis. These factors collectively contribute to the progression of cardiovascular disease (34). The weight of each individual was measured by personal balance without heavy clothes and shoes. The height also was measured by tape measure, and then body mass index was estimated according to the world health organization (WHO) classification.[35]

The results of our study were agreed with the survey,[36] The literature indicates that an elevated BMI is linked to many noteworthy health consequences, such as hypertension (HTN), DM, metabolic syndrome (MetS), and dyslipidemia. These conditions are recognised as independent risk factors for CVD. The findings of our investigation were in alignment with the results obtained.[37] The study shown that persons with a higher BMI have a higher prevalence, extent, and severity of CVD. The findings of our investigation are incongruous with the existing body of literature,[38,39] which reported an inverse relationship between BMI and CVD. With increasing age, there is a favourable correlation between the prevalence of diabetes and pre-diabetes. By evaluating HbA1c levels, post-meal hyperglycemia, a first sign of diabetes, may be evaluated. Elevated HbA1c readings are a sign that you're more likely to have diabetes in the future.[40] A significant relationship exists between HbA1c and insulin resistance, whereas HbA1c has shown a stronger association with insulin sensitivity in individuals who possess normal glucose tolerance and are in good health.[40,41] Furthermore, it has been hypothesised that insulin resistance has a significant and autonomous role in the susceptibility to type 2 diabetes mellitus and cardiovascular ailments;[42,43] Several different approaches have been developed as surrogate measures of insulin resistance in order to distinguish people with different degrees of insulin sensitivity, given the intrusive nature of directly assessing insulin resistance.[44,45] Nevertheless, it is worth noting that these indices fail to provide insight into the glycemic condition over a period of 2-3 months, a timeframe that is significantly linked to insulin resistance. Hence, it is important to establish the precise function of HbA1c as a surrogate marker for insulin resistance and determine the most effective threshold value. This will enable the implementation of timely treatments, such as lifestyle adjustments, in order to address the issue at an early stage.

This research, consisting of a sample size of 176 individuals, revealed that heightened levels of insulin resistance, glucose, HOMA IR, and HbA1c at the first assessment were indicative of the development of Type 2 diabetes over time. The presented data demonstrates that there exists variability in the association between glucose and HbA1c, as well as insulin sensitivity, among different populations. The observed heightened risk persisted regardless of other diabetes risk variables, such as age, gender, body mass index (BMI), and serum triglyceride levels.

Additionally, individuals with diabetes mellitus (DM) and cardiovascular disease (CVD) showed a compensatory increase in plasma insulin levels and rates of insulin secretion. This reaction might be related to changes in the expression of vital enzymes involved in glucose metabolism as well as an increase in the cell mass.[46] Microalbuminuria is considered a potential marker for microvascular illness that arises due to extensive damage to glomerular endothelial cells.[47] Furthermore, this topic has garnered significant interest due to its strong correlation with several issues related to macrovascular diseases.[48] The current investigation demonstrated a statistically significant inverse correlation between the specified variables (TG/ TC and LDL) and the marker of insulin resistance (HOMA-IR) in persons with cardiovascular disease and diabetes mellitus, as well as a strong inverse correlation with indicators of insulin sensitivity.

The coexistence of impaired fasting glucose (IFG) and elevated HbA1c levels demonstrated a robust predictive capacity for diabetes, hence facilitating the identification of people who may benefit from targeted preventative interventions. Fasting blood sugar (FBS) and glycated haemoglobin (HbA1c) may potentially represent distinct facets of glucose metabolism. One aspect to consider is that there exists a stronger association between postprandial plasma glucose levels and HbA1c compared to fasting blood sugar levels[49] and depend upon insulin resistance, hepatic glucose output uptake and insulin secretion capacity of pancreatic B-cells.[50,51] Therefore, HbA1c has the ability to indicate many aspects of glucose metabolism. In contrast, the levels of FBS are mostly influenced by insulin resistance and hepatic glucose synthesis.[52]

Table 1. Demographic characteristics of control subjects and other Groups.

Characteristic	Control	DM	CVD and DM	P Value
	n=60	n=60	n=60	
Age(years)				
Range	40- 80	40 - 80	40 - 80	0.0760
Mean±SEM	54.72±1.405	56.02±1.395	59.20±1.478	ns
BMI (kg/m^2)				
Range	21.78 - 26.81	22.03 - 28.4	22.84 - 29.78	<0.0001
Mean±SEM	24.56±0.1985	25.28±0.2454	27.13±0.2501	****
Gender				
Male, *n* (%)	30 (50.0 %)	30 (50.0 %)	30 (50.0 %)	0.9723
Female, *n* (%)	30 (50.0 %)	30 (50.0 %)	30 (50.0 %)	ns

n: number of cases; SEM: Standard Error of Mean; ns: not significant at p > 0.05 ;
****: significant at *p* <0.0001

Table 2. Comparison of mean values of the studied biomarkers among the control group and other groups.

Characteristic	Control	DM	CVD and DM	P Value
	n=60	n=60	n=56	
Glucose (mg/dL)				
Range	78.91-121.7	184.3-309.3	194-484.7	<0.0001
Mean±SEM	97.68±1.014	227.0±6.053	301.6±9.620	****
Hemoglobin A1c%				
Range	4.11 - 5.93	7.06 - 13.6	7.85-14.88	<0.0001
Mean±SEM	4.917±0.06139	9.165±0.2329	12.08±0.2337	****
Insulin (mIU/ml)				
Range	3.69-11.95	11.6-31.35	18.95-38.3	<0.0001
Mean±SEM	7.314±0.2871	20.40±0.6199	26.49±0.5756	****
HOMA IR				
Range	0.7592-2.951	5.676-20.97	11.00-35.34	<0.0001
Mean±SEM	1.768±0.07192	11.61±0.5459	19.74±0.7800	****
TNFα (pg/mL)				
Range	19.07-67.59	47.87-195.6	70.37-195.6	<0.0001
Mean±SEM	36.42±1.448	119.5±5.091	132.4±3.918	****

n: number of cases; SEM: Standard Error of Mean; TNFα : Tumor Necrosis Factor Alpha;
****: significant at *p* <0.0001

Consequently, the use of both FBS and HbA1c measurements may include a broader spectrum of pathophysiological mechanisms in diabetes compared to the use of either measurement in isolation. Hence, it can be concluded that the use of HbA1c in conjunction with other factors enhances the ability to forecast cardiovascular disease (CVD) in individuals diagnosed with diabetes. However, it is worth noting that this particular combination demonstrates more efficacy in patients with diabetes mellitus (DM)

The rise of HbA1C may be elucidated as follows: Elevated levels of blood glucose induce several metabolic and structural disruptions inside the vasculature. The phenomenon via which glucose induces these potentially detrimental alterations is referred to as glycation. The process of glucose binding with protein residues, such as lysine and arginine, leads to the formation of Amadori complexes. One prominent example of an Amadori complex is HbA1c. Subsequently, these complexes undergo transformation into advanced glycation end-products (AGEs) by oxidative, non-oxidative, and spontaneous mechanisms. These particular compounds undergo a reaction with the haemoglobin present in the bloodstream, resulting in the formation of hemoglobin-AGE. The concentrations of these products are shown to be higher in individuals diagnosed with diabetes. AGE products have the ability to interact with their corresponding receptors, known as RAGE, which are found on smooth muscle cells, endothelial cells, and immune system cells. This interaction leads to the induction of oxidative stress.[53] The presence of elevated hepatic fat content has been shown to be correlated with insulin resistance, irrespective of an individual's total adiposity.[54] The differentiation of white blood cells is primarily determined by the secretion of cytokines, with a particular emphasis on interleukin-6. Insulin has a pronounced and immediate anti-inflammatory action, characterised by the suppression of pro-inflammatory cytokines.[55] Lifestyle adjustment has been shown to be effective in managing Impaired Glucose Tolerance (IGT), which is recognised as the only pre-diabetic glucose category.

This research conducted a thorough analysis to investigate the relationships between levels of Tumour necrosis factor alpha (TNFα) and the most prevalent CVD among a general population. The findings of this study demonstrated favourable connections between TNFα levels and both diabetes mellitus and cardiovascular disease. The identification of TNFα as a circulating cytokine with anti-tumorigenic properties occurred in 1975.[56] Initially, it was believed that immune cells like activated macrophages and lymphocytes generated the majority of TNFα, but further investigations have shown that it is also expressed by endothelial and epithelial cells, smooth muscle cells, and cardiac myositis.[57]

Recent research has shown that TNFα plays a vital role as a pro-inflammatory cytokine and is a critical element of the innate immune system. It facilitates the upregulation of genes that are needed for the regulation of tissue inflammation and damage in response to the activation of pattern recognition receptors.[58] Atherothrombotic disease is a chronic inflammatory condition affecting the artery wall, which has been shown to be triggered by TNFα. One potential favourable correlation between TNFα and ischemic stroke.[59,60]

TNFα levels were higher in CVD and diabetes patients compared to DM. patients and controls, respectively, and there was a significant difference in TNFαlpha concentrations across study groups (p-value < 0.0001). The results of this research show that those who are more likely to have repeated coronary episodes had elevated plasma concentrations of TNFα, a cytokine with several systemic effects, for several months following myocardial infarction (MI).[61]

Previous studies on acute myocardial infarction (MI) suggest that the peri-infarct region's inflammatory cells are the main source of cytokines. As a result, an increased inflow of inflammatory cells is blamed for long-term increases in cytokine levels.[62,63] On the other hand, a recent experimental study looked at myocardial infarction (MI) brought on by rat left anterior descending coronary artery occlusion. The research found that TNFα expression persisted in the myocardium even in myocardial segments that were otherwise thought to be normal following the onset of infarction.[64,65] The study showed that TNFα gene and protein expression persisted for a long time in myocytes, suggesting a possible long-term involvement of this cytokine in the process of vascular remodelling.[66] The findings suggest that more experimental studies are required to determine the cause of the observed elevations in TNFα levels.

Previous researchers have posited that the continued presence of TNFα throughout the latter stages of MI might potentially have a role in the loss of cardiac myocytes and subsequent cardiac decompensation.[67] In our dataset, it was discovered that patients with higher levels of TNFA were more likely to die from coronary disease and have recurrent MI. These results thus lend credence to the idea that inflammation plays a substantial role in the development of acute coronary syndromes, [68,69] as well as having long-term prognostic value among apparently stable patients.[70,71] Ultimately, the findings of this study suggest that individuals with heightened levels of TNFα face a higher risk of developing acute coronary occlusion, regardless of other risk factors. Consequently, these results lend support to the notion that innovative treatments aimed at reducing the inflammatory response following such occlusions could potentially offer a novel approach to managing myocardial infarction.[68,69]

The potential mechanism underpinning TNFα-induced atherothrombosis encompasses many hypothesised pathways, such as its potential positive impact on circulating lipids, insulin resistance, endothelial dysfunction, leukocyte recruitment, oxidative stress, vasodilation, or coagulation.[72] The pathogenesis of venous thromboembolism is distinct from that of arterial thrombosis, since the former is primarily influenced by the development of atherosclerosis. Although the involvement of inflammation and the innate immune system in the pathogenesis of venous thromboembolism is well recognised, the precise relationship between TNFα and the process of thrombogenesis needs to be fully elucidated. On the one hand, it has been suggested that TNFα may contribute to the promotion of a pro-coagulant condition.[73]

CONCLUSION

Based on the findings of this research, it can be inferred that TNFα and HbA1c have the potential to serve as practical and straightforward indicators for predicting the simultaneous occurrence of insulin resistance, dysglycemia, and Cardiovascular diseases in a community of seemingly healthy individuals under the age of 50 in Al-Basra. The objective of this study was to assess the comparative effectiveness of TNFα, HbA1c, insulin resistance, and glucose as surrogate markers of insulin resistance in identifying asymptomatic individuals with an atherogenic lipoprotein profile, thereby increasing their susceptibility to cardiovascular disease. The study employed standardised reference values, ensuring its clinical applicability across different geographical regions.

REFERENCES

1. Ilyas IK, Volha T. Insulin Resistance and their Affects on Biochemical Parameters of Cardiovascular Risk Factors. The Review of Diabetic Studies. 2023 Oct 1;19(2)..
2. Yunir E, Wisman BA, Antono D, Mansjoer A, Sarumpaet A, Iswati E, Rosana M, Tahapary DL, Tarigan TJ, Soewondo P. Factors Affecting Mortality of Critical Limb Ischemia 1 Year after Endovascular Revascularization in Patients with Type 2 Diabetes Mellitus. Review of Diabetic Studies. 2022 Mar 9;18(1):20-6..
3. Mohanty L, Sahoo D, Meher D, Sahoo P. Prevalence of diabetes in patients with myocardial infarction: a study in a tertiary care centre. Int J Adv Med. 2016;3(4):842–6.
4. Khattab MH, Shahwan MJ, Hassan NA, Jairoun AA. Abnormal High-sensitivity C-reactive Protein is Associated with an Increased Risk of Cardiovascular Disease and Renal Dysfunction among Patients Diagnosed with Type 2 Diabetes Mellitus in Palestine. Review of Diabetic Studies. 2022 Mar 9;18(1):27-33.
5. Natarajan J, Mokoboto-Zwane S. Health-related quality of life and domain-specific associated factors among patients with Type2 diabetes mellitus in south India. Review of Diabetic Studies. 2022 Mar 9;18(1):34-41.
6. Janssen JA. Hyperinsulinemia and its pivotal role in aging, obesity, type 2 diabetes, cardiovascular disease and cancer. Int J Mol Sci. 2021;22(15):7797.
7. Ruige JB, Assendelft WJJ, Dekker JM, Kostense PJ, Heine RJ, Bouter LM. Insulin and risk of cardiovascular disease: a meta-analysis. Circulation. 1998;97(10):996–1001.
8. Christiansen CB, Mellbye FB, Hermansen K, Jeppesen PB, Gregersen S. Effects of Aronia melanocarpa on cardiometabolic diseases: A systematic review of quasi-design studies and randomized controlled trials. Review of Diabetic Studies. 2022 Jun 30;18(2):76-92..
9. Media AH, Al Abachi SZ. Impact of diabetes mellitus on serum irisin level and other biochemical parameters. Medicinski časopis. 2023;57(1):21-6..
10. Eddy D, Schlessinger L, Kahn R, Peskin B, Schiebinger R. Relationship of insulin resistance and related metabolic variables to coronary artery disease: a mathematical analysis. Diabetes Care. 2009;32(2):361–6.
11. Yun J-S, Ko S-H. Current trends in epidemiology of cardiovascular disease and cardiovascular risk management in type 2 diabetes. Metabolism. 2021;123:154838.
12. Ahlqvist E, Prasad RB, Groop L. Subtypes of type 2 diabetes determined from clinical parameters. Diabetes. 2020;69(10):2086–93.
13. Monaco C, Nanchahal J, Taylor P, Feldmann M. Anti-TNF therapy: past, present and future. Int Immunol. 2015;27(1):55–62.
14. Siti HN, Kamisah Y, Kamsiah J. The role of oxidative stress, antioxidants and vascular inflammation in cardiovascular disease (a review). Vascul Pharmacol. 2015;71:40–56.
15. Yuan T, Yang T, Chen H, Fu D, Hu Y, Wang J, Yuan Q, Yu H, Xu W, Xie X. New insights into oxidative stress and inflammation during diabetes mellitus-accelerated atherosclerosis. Redox biology. 2019 Jan 1;20:247-60.
16. Kelleher RJ, Soiza RL. Evidence of endothelial dysfunction in the development of Alzheimer's disease: Is Alzheimer'sa vascular disorder? Am J Cardiovasc Dis. 2013;3(4):197.
17. Shephard MT, Merkhan MM, Forsyth NR. Human Mesenchymal Stem Cell Secretome Driven T Cell Immunomodulation Is IL-10 Dependent. International Journal of Molecular Sciences. 2022 Nov 6;23(21):13596.

18. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia. 1985;28:412–9.
19. Shao C, Wang J, Tian J, Tang Y. Coronary artery disease: from mechanism to clinical practice. Coron Artery Dis Ther Drug Discov. 2020;1–36.
20. Samanidis G, Gkogkos A, Bousounis S, Zoumpourlis P, Perrea D, Perreas K. Risk factors for severity of coronary artery disease in patients with cardiovascular disease. Atherosclerosis. 2021;331:e104–5.
21. Foody JM, Milberg JA, Pearce GL, Sprecher DL. Lipoprotein (a) associated with coronary artery disease in older women: age and gender analysis. Atherosclerosis. 2000;153(2):445–51.
22. Mancheva M, Paljoskovska-Jordanova S, Bosevski M. Carotid intima media thickness is in a relation to risk factors for coronary artery disease. Arter Hypertens. 2020;183(27):8.
23. Rodgers JL, Jones J, Bolleddu SI, Vanthenapalli S, Rodgers LE, Shah K, Karia K, Panguluri SK. Cardiovascular risks associated with gender and aging. Journal of cardiovascular development and disease. 2019 Apr 27;6(2):19.
24. Forman DE, Rich MW, Alexander KP, Zieman S, Maurer MS, Najjar SS, Cleveland JC, Krumholz HM, Wenger NK. Cardiac care for older adults: time for a new paradigm. Journal of the American College of Cardiology. 2011 May 3;57(18):1801-10.
25. Ikäheimo TM. Cardiovascular diseases, cold exposure and exercise. Temperature. 2018;5(2):123–46.
26. Wang M, Tan Y, Shi Y, Wang X, Liao Z, Wei P. Diabetes and sarcopenic obesity: pathogenesis, diagnosis, and treatments. Front Endocrinol (Lausanne). 2020;11:568.
27. Jiang T, Zhang Y, Dai F, Liu C, Hu H, Zhang Q. Advanced glycation end products and diabetes and other metabolic indicators. Diabetol Metab Syndr. 2022;14(1):104.
28. Yan Z, Cai M, Han X, Chen Q, Lu H. The Interaction Between Age and Risk Factors for Diabetes and Prediabetes: A Community-Based Cross-Sectional Study. Diabetes, Metab Syndr Obes. 2023;85–93.
29. Forman DE, Rich MW, Alexander KP, Zieman S, Maurer MS, Najjar SS, Cleveland JC, Krumholz HM, Wenger NK. Cardiac care for older adults: time for a new paradigm. Journal of the American College of Cardiology. 2011 May 3;57(18):1801-10.
30. Verdoia M, Schaffer A, Barbieri L, Bellomo G, Marino P, Sinigaglia F, Suryapranata H, De Luca G. Impact of age on mean platelet volume and its relationship with coronary artery disease: a single-centre cohort study. Experimental Gerontology. 2015 Feb 1;62:32-6.
31. Sabah KM, Chowdhury AW, Khan HL, Hasan AH, Haque S, Ali S, Kawser S, Alam N, Amin G, Mahabub SE. Body mass index and waist/height ratio for prediction of severity of coronary artery disease. BMC research notes. 2014 Dec;7:1-7.
32. Nabati M, Moosazadeh M, Soroosh E, Shiraj H, Gholami M, Ghaemian A. Correlation between overweightness and the extent of coronary atherosclerosis among the South Caspian population. BMC Cardiovasc Disord. 2020;20:1–11.
33. Qu YN, Zhang F, Li C, Dai Y, Yang H, Gao Y, Pan Y, Yao K, Huang D, Lu H, Ma J. Relationship between body mass index and outcomes of coronary artery disease in Asian population: Insight from the FOCUS registry. International journal of cardiology. 2020 Feb 1;300:262-7.
34. Jahangir E, De Schutter A, Lavie CJ. The relationship between obesity and coronary artery disease. Transl Res. 2014;164(4):336–44.
35. Kibr G. Food Choice Behaviors of Lactating Women: Association with Body Mass Index and Fruits and Vegetables Intake in Central Amhara Region, Ethiopia—An Observational Study. J Nutr Metab. 2021;2021.
36. Alkhawam H, Nguyen J, Sayanlar J, Sogomonian R, Desai R, Jolly J, Vyas N, Syed U, Homsi M, Rubinstein D. Coronary artery disease in patients with body mass index≥ 30 kg/m2: a retrospective chart analysis. Journal of community hospital internal medicine perspectives. 2016 Jan 1;6(3):31483.
37. Labounty TM, Gomez MJ, Achenbach S, Al-Mallah M, Berman DS, Budoff MJ, Cademartiri F, Callister TQ, Chang HJ, Cheng V, Chinnaiyan KM. Body mass index and the prevalence, severity, and risk of coronary artery disease: an international multicentre study of 13 874 patients. European Heart Journal–Cardiovascular Imaging. 2013 May 1;14(5):456-63.
38. Rubinshtein R, Halon DA, Jaffe R, Shahla J, Lewis BS. Relation between obesity and severity of coronary artery disease in patients undergoing coronary angiography. Am J Cardiol. 2006;97(9):1277–80.
39. Niraj A, Pradahan J, Fakhry H, Veeranna V, Afonso L. Severity of coronary artery disease in obese patients undergoing coronary angiography:"obesity paradox" revisited. Clin Cardiol An Int Index Peer-Reviewed J Adv Treat Cardiovasc Dis. 2007;30(8):391–6.
40. Devaraj NK, Rashid AA, Jamari MS, Sharif NF, Paramesvaran R. Knowledge, Attitude, Practice and Awareness on Hypertension among Students and Staffs in Faculty Of Medicine and Health Sciences (Fmhs), Universiti Putra Malaysia. Malta Medical Journal. 2023 Nov 8;35(2).: 51-56
41. Schembri B, Falzon ML, Casingena L, DeGiorgio G, Grech Sciberras M, Manfre M, Cassar K. Adequacy of clinical surveillance of diabetic patients requiring minor foot amputations. Malta Medical Journal. 2022;34(1): 76-86.
42. Alsadoon L, Abdullah K. Comparative effect of insulin, glimepiride, and metformin on inflammatory markers in type 2 diabetes mellitus. Georgian Medical News. 2023 Feb 1(335):60-3.
43. Didenko S, Subbotin V, Hupalo Y, Ivanko O, Orlych O. Study of the hemomicrocirculatory channel in patients with diabetes and threatening ischemia of the lower limb. Georgian Medical News. 2023 Apr 1(337):85-8..
44. Klimontov V, Mavlianova K, Semenova J, Orlov N. Circulating peptides of the tnf superfamily and tnf receptor superfamily in subjects with type 1 diabetes: relationships with clinical and metabolic parameters. Georgian Medical News. 2023 Jul 1(340-341):243-8..
45. Ahmed HS, Hilal NN, Zakari MG. Evaluation of vitamin K2 in patients with type 2 diabetes mellitus. Georgian Medical News. 2023 Oct, (343): 14-17.
46. Younis HY, Thanoon IA, Fadhil NN, Merkhan MM. Effect of zinc as an add-on to metformin therapy on glycemic control, serum insulin, and c-peptide levels and insulin resistance in type 2 diabetes mellitus patient. Research Journal of Pharmacy and Technology. 2022;15(3):1184-8..
47. Younis HY, Imad A. Effect of zinc as an add on to metformin therapy on serum lipid profile and uric acid in type 2 diabetes mellitus patients. Curr topics in Pharmacology. 2021;25.
48. Livingston EH. The Role of Bariatric Surgery in Managing the Macrovascular Complications of Obesity-Related Type 2 Diabetes. JAMA. 2019;322(13):1259–60.
49. Dubey D, Kunwar S, Gupta U. Mid-trimester glycosylated hemoglobin levels (HbA1c) and its correlation with oral glucose tolerance test (World Health Organization 1999). J Obstet Gynaecol Res. 2019;45(4):817–23.
50. Merkhan MM. The effects of glibenclamide on thyroid function tests in type 2 diabetic patients. Iraq J Pharm Vol. 2013;13(2).
51. Merkhan MM, Abdullah KS. The role of vitamin C and E in improving hearing loss in patients with type 2 diabetes. Annals of the College of Medicine, Mosul. 2020 Jan 29;41(2):184-9.

52. Merkhan MM. Effect of metformin, glibenclamide and insulin on lipid profile in type 2 diabetic patients. Tikrit Journal of Pharmaceutical Sciences. 2013;9(2):262-9.

53. Johnson J, Jaggers RM, Gopalkrishna S, Dahdah A, Murphy AJ, Hanssen NM, Nagareddy PR. Oxidative stress in neutrophils: implications for diabetic cardiovascular complications. Antioxidants and redox signaling. 2022 Apr 1;36(10):652-66.

54. Tricò D, Galderisi A, Mari A, Polidori D, Galuppo B, Pierpont B, Samuels S, Santoro N, Caprio S. Intrahepatic fat, irrespective of ethnicity, is associated with reduced endogenous insulin clearance and hepatic insulin resistance in obese youths: A cross-sectional and longitudinal study from the Y ale P ediatric NAFLD cohort. Diabetes, Obesity and Metabolism. 2020 Sep;22(9):1628-38.

55. Mohammad JA, Fathi FH, Almulathanon AA, Merkhan MM. Hyperlipidemia connoted vitiation of serum adipokines and redox imbalances. Military Medical Science Letters/Vojenské Zdravotnické Listy. 2023 Apr 1;92(2).

56. Carswell E, Old LJ, Kassel R, Green S, Fiore N, Williamson B. An endotoxin-induced serum factor that causes necrosis of tumors. Proc Natl Acad Sci. 1975;72(9):3666–70.

57. Steinhoff MS, von Mentzer B, Geppetti P, Pothoulakis C, Bunnett NW. Tachykinins and their receptors: contributions to physiological control and the mechanisms of disease. Physiol Rev. 2014;94(1):265–301.

58. Pascual M, Calvo-Rodriguez M, Núñez L, Villalobos C, Ureña J, Guerri C. Toll-like receptors in neuroinflammation, neurodegeneration, and alcohol-induced brain damage. IUBMB Life. 2021;73(7):900–15.

59. Li X, Guo D, Hu Y, Zhou H, Chen Y. Potential Biomarkers and Therapeutic Targets: Inflammation and Oxidative Stress in Left Carotid Artery Stenosis with Coronary Artery Disease. Curr Pharm Des. 2023;29(12):966–79.

60. Ait-Oufella H, Libby P, Tedgui A. Anticytokine immune therapy and atherothrombotic cardiovascular risk. Arterioscler Thromb Vasc Biol. 2019;39(8):1510–9.

61. Guo R, Wu T, Zheng N, Wan Y, Wang J. Clinical Features of Acute Coronary Syndrome in Patients with Coronary Heart Disease and Its Correlation with Tumour Necrosis Factor in Cardiology. Comput Math Methods Med. 2022;2022.

62. Peet C, Ivetic A, Bromage DI, Shah AM. Cardiac monocytes and macrophages after myocardial infarction. Cardiovasc Res. 2020;116(6):1101–12.

63. Ma Y, Yang S, He Q, Zhang D, Chang J. The role of immune cells in post-stroke angiogenesis and neuronal remodeling: the known and the unknown. Front Immunol. 2021;12:784098.

64. Han X, Yang Y, Zhang M, Li L, Xue Y, Jia Q, Wang X, Guan S. Liquiritin protects against cardiac fibrosis after myocardial infarction by inhibiting CCL5 expression and the NF-κB signaling pathway. Drug Design, Development and Therapy. 2022 Jan 1:4111-25.

65. Ning Y, Huang P, Chen G, Xiong Y, Gong Z, Wu C, Xu J, Jiang W, Li X, Tang R, Zhang L. Atorvastatin-pretreated mesenchymal stem cell-derived extracellular vesicles promote cardiac repair after myocardial infarction via shifting macrophage polarization by targeting microRNA-139-3p/Stat1 pathway. BMC medicine. 2023 Dec;21(1):1-8.

66. Silveira Rossi JL, Barbalho SM, Reverete de Araujo R, Bechara MD, Sloan KP, Sloan LA. Metabolic syndrome and cardiovascular diseases: Going beyond traditional risk factors. Diabetes Metab Res Rev. 2022;38(3):e3502.

67. Matsumori A. Targeting inflammation in the diagnosis, management, and prevention of cardiovascular diseases. Glob Heart. 2022;17(1).

68. Merkhan M, Mohammad J, Fathi Z, Younus Z, Mahmood SM, Mohammed M. Silent hyperlipidaemia modulated vascular endothelial markers. Pharmacia. 2021 Oct 6;68(2):479-84.

69. Fuadi MR, Nugraha J, Suryawan IG, Kahar H, Prabowo GI, Utomo B, I'tishom R. Correlation of Apo E Gene Polymorphism with Recurrent Acute Coronary Syndrome. Pharmacognosy Journal. 2023;15(3)..

70. Ridker PM, Glynn RJ, Hennekens CH. C-reactive protein adds to the predictive value of total and HDL cholesterol in determining risk of first myocardial infarction. Circulation. 1998;97(20):2007–11.

71. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. N Engl J Med. 1997;336(14):973–9.

72. Yuan S, Carter P, Bruzelius M, Vithayathil M, Kar S, Mason AM, Lin A, Burgess S, Larsson SC. Effects of tumour necrosis factor on cardiovascular disease and cancer: A two-sample Mendelian randomization study. EBioMedicine. 2020 Sep 1;59.

73. Neto BV, Tavares V, Santos JMO, Cerqueira F, Pereira D, Medeiros R. Map of thrombogenesis in viral infections and viral-driven tumours. Discov Oncol. 2023;14(1):3.

Cite this article: Jabber HN, Charfeddine B, Abbas HJ. Evaluation of Tumor Necrosis Factor Alpha, Insulin, glucose, HbA1c% and HOMA-IR as Predictors for Cardiovascular Diseases in Patients with Type 2 Diabetes. Pharmacogn J. 2024;16(1): 195-201.