BioScientific Review (BSR)
Volume 6 Issue 1, 2024
ISSN$_{(P)}$: 2663-4198 ISSN$_{(E)}$: 2663-4201
Homepage: https://journals.umt.edu.pk/index.php/bsr

Article QR

Title:	**Exploring Atherosclerosis, Oxidized LDL, Insulin, and Tailored Diet Strategies in Cardiac Patient Assessment**
Author (s):	Faiza Tariq[1], Syeda Hira Moazzam[2], Eisha Youman[2], Sobia Mushtaq[3]
Affiliation (s):	[1]Government College University Faisalabad (Sahiwal Campus), Pakistan [2]University of Sialkot, Sialkot, Pakistan [3]Pir Mehar Ali Shah Arid Agriculture University, Rawalpindi, Pakistan
DOI:	https://doi.org/10.32350/bsr.61.04
History:	Received: August 14, 2023, Revised: November 4, 2023, Accepted: December 8, 2023, Published: January 30, 2024
Citation:	Tariq F, Moazzam SH, Youman E, Mushtaq S. Exploring atherosclerosis, oxidized LDL, insulin, and tailored diet strategies in cardiac patient assessment. *BioSci Rev*. 2024;6(1):95–108. https://doi.org/10.32350/bsr.61.04
Copyright:	© The Authors
Licensing:	This article is open access and is distributed under the terms of Creative Commons Attribution 4.0 International License
Conflict of Interest:	Author(s) declared no conflict of interest

A publication of
The Department of Life Sciences, School of Science
University of Management and Technology, Lahore, Pakistan

Exploring Atherosclerosis, Oxidized LDL, Insulin, and Tailored Diet Strategies in Cardiac Patient Assessment

Faiza Tariq[1*], Syeda Hira Moazzam[2], Eisha Youman[2], Sobia Mushtaq[3]

[1]Department of Food Sciences, Government College University Faisalabad, Sahiwal Campus, Pakistan

[2]University of Sialkot, Pakistan
[3]Institute of Biochemistry and Biotechnology, Pir Mehar Ali Shah Arid Agriculture University, Rawalpindi, Pakistan

ABSTRACT

Background Plaque development in vessels which supply blood to heart muscles is caused by atherosclerosis, a slow but progressive process that leads to coronary artery disease (CAD). Arteries become gradually blocked by oxidized fatty acids, with excess fat intake or abnormalities in fat metabolism causing body changes. These changes may lead to an increase in LDL cholesterol, triglycerides, as well as a reduction in HDL cholesterol. The oxidation of excess low density protein (LDL) is a complex process involving many factors, with insulin and obesity playing a significant role and associated with many metabolic syndromes. The current study aims to determine the concentration of oxidized LDL in patients who suffer with cardio vascular diseases (CVDs) and to understand the correlation between oxidation and insulin resistance in cardiac forbearing.

Method The method used was to collect data from 30 patients admitted in the cardiology ward. For this purpose, an assessment proforma was built, which included anthropometric measurements, physical activity level, dietary history, and blood tests for lab findings such as lipid profiles.

Results The key findings determined that the anomalous function of AKT protein, which is present in pancreatic β cells, as well as disruption in PKC pathway cause phosphorylation in alpha and beta cells of pancreas, which causes diabetes and leads to heart attack.

Conclusion The aberrant changes in sugar test and lipid profile including Hb1Ac (9%), fasting blood glucose (250mg/dl), total cholesterol (342mg/dl), LDL (less than 250mg/dl), HDL (49 F mg/dl), and total triglycerides (215mg/dl) causes serious discomfort for patients.

Keywords: cardio vascular disease (CVD), insulin resistance, lipid abnormalities, low density protein (LDL), metabolic syndrome, oxidized LDL

Highlights

- Metabolic syndromes cause atherosclerosis and disturb the total cholesterol level in human body.

*Corresponding Author: faizat872@gmail.com

- The analysis mainly aims to understand the relationship between low density lipoprotein (LDL) and insulin.
- Anthropometric measurements, physical activity level, dietary history, and blood tests for lab findings were used to observe and evaluate results.
- Variation in lab findings observed and disruption in PKC pathway are the causes of phosphorylation in alpha and beta cells of pancreas.

1. INTRODUCTION

Cardio vascular diseases (CVDs) have been held responsible for the most important increase in death rate during the last 20 years worldwide, resulting in over two million deaths. It is noteworthy that ischemic heart disease is accountable for the most significant surge in mortality rate [1].

CVD is an umbrella term that includes a wide range of interconnected conditions that affect heart and its connecting vessels. Some important diseases include chronic heart disease, atherosclerosis, hypertension, ischemic heart disease, peripheral vascular disease, and heart failure. These maladies frequently coexist in approximately one-third of adults affected by CVD (see Figure 1) [1].

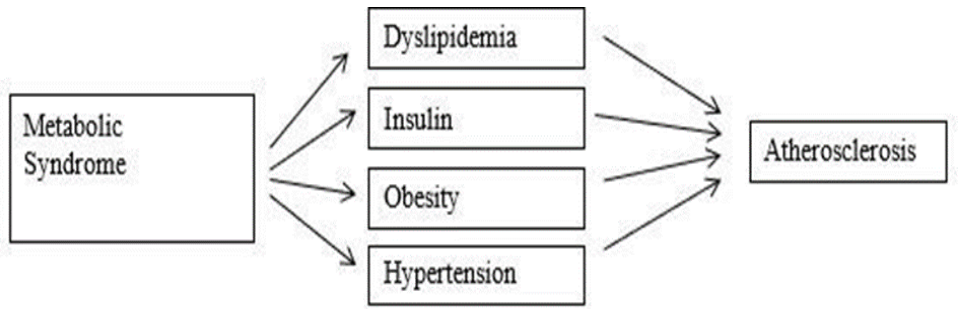

Figure 1. Diagram Showing Which Metabolic Syndrome Causes Atherosclerosis

To determine dyslipidemia, a lipid profile analysis is essential to evaluate the precise low density lipoprotein (LDL), high density lipoprotein (HDL), and cholesterol and triglyceride levels. To identify hypertension, blood pressure values eclipse 140/90 mmHg, while the American Diabetes Association recommends that individuals with diabetes exhibit glucose levels exceeding 126 mg/dl [2].

Diabetes Mellitus (DM) Type 2 is the most prevalent form of metabolic disorder and is frequently expressed by chronic hyperglycemia (high glucose level in blood), hyperinsulinemia (high insulin level in blood), hyperlipidemia (high level of lipid in blood), and lipotoxicity (deleterious effects of lipid accumulation in non-adipose tissues), which leads to a progressive decline in insulin secretion and action [3]. The excess production of free radicals including oxidants has been linked to the cause or occurrence of diabetes, resulting in hyperglycemia [4]. Insulin resistance (a metabolic disorder) plays a crucial role in production or becomes the main cause of DM Type 2. The often-seen determinants consist of hyperinsulinemia, decreased HDL cholesterol, upraised triglyceride, and hypertension with insulin resistance [5].

Lipocytes (also called fat cells), insulin resistance, and inflammation or swelling have been reported as significant indicators of DM Type 2 [6].

Insulin resistance is typified by a reduction in peripheral glucose uptake. This is an important administrative point in controlling or managing blood glucose, particularly in the musculature, as well as any concomitant elevation in endogenous or cell interior glucose production. Furthermore, diminishing peripheral glucose utilization or uptake and weakening beta-cell working leads to chronic hyperglycemia [7].

Under normal circumstances, glucose uptake occurs inside the cells, as shown in Figure 1. However, in insulin resistance (which is a metabolic disorder), insulin receptor cells become more resistant to insulin, causing elevated insulin and glucose volume in the bloodstream or blood vessels. This may lead to disruption in glucose metabolism known as glycolysis, resulting in an elevated amount of glucose in blood, oxidative stress, and inflammatory responses, which is a fundamental type of response after any disease that causes cellular damage or necrosis. Due to the high concentration of glucose in the blood, LDL is exposed or revealed in front of extreme levels of circulating blood glucose, which changes LDL to glycated LDL [8].

Elevation in food intake, from organic healthy foods which are additive and chemical free to healthy foods, may result in increased exposure to leading advanced glycated end products (AGEs) caused by a non-enzymatic chain reaction called glycation. Industries or professionals use AGEs to enhance flavor or taste, color, and shelf life of food items. However, high exposure to these AGEs may refer to or become a serious health breakdown. Serum endogenous advance glycated end products (sAGEs), produced within the body along with digestion, absorption, and metabolism, as well as exogenous AGEs also called dietary AGEs (dAGEs), are two types of AGEs. Both endogenous (inside) and exogenous (outside) AGEs significantly contribute to the body's AGE pool [9].

Various studies give brief details about the fact that old-age people are exposed to both endogenous and exogenous AGEs, which causes the growth and enhancement of severe health disturbance, as well as interfere and correlates with oxidative stress (due to free radicals and inflammation). Elevated consumption of processed and deep-fried comestibles, as well as high fructose products, has been linked to the onset of swelling and disruption of the immune system. The key anatomical consequences of insulin on nutrient consumption in human beings occur after eating meals when the level of blood glucose rises which enhances the secretion of insulin from pancreas. Consequently, glucose is uptaken from plasma and utilized by muscle cells and the adipose tissue. Hepatic glucose secretion decreases with a corresponding decrease in gluconeogenesis, lipogenesis, and glycogenolysis [10].

2. MATERIALS AND METHOD

Prior to the collection of blood samples, appropriate authorization was obtained from authorized bodies and patients were informed accordingly. All research activities were conducted at Sheikh Zayed Hospital Lahore. A human-based empirical study was conducted under the supervision of a designated supervisor. The study was completed

within a period of 4 to 5 months in the year 2023.

Blood samples (almost 5ml) were collected and analyzed from a total of 30 cardiac patients at Sheikh Zayed Hospital Lahore (cardiology ward), although the results are based only on one patient's data. Blood samples were collected from patients who met the specified inclusion criteria/measurement standards, such as patients (from any age or gender) with a history of heart disease, hypertension, and obesity. Patients with end stage cardiomyopathy and with serious conditions were excluded from the study.

A glucometer, which requires only a small drop of blood, was utilized for blood glucose testing. The portability of the device renders it highly versatile, as it can be employed in any given setting. Detailed instructions for device operation were provided. Additionally, guidance of a health professional or caregiver, such as an endocrinologist or certified diabetic educator, may be sought on disease management, meal planning, and other related topics [11].

Different blood sugar and lipid profile tests were performed including Hb1Ac, Fasting Blood Glucose, Lipid Profile Test, Total Cholesterol, LDL, HDL, Total Triglycerides, and Ox. LDL Test.

Table 1. Normal Ranges of Laboratory Tests

Sr. No	Test Name	Normal Ranges	Unit
1	Hb1Ac	4-5.6	%
2	Fasting Blood Glucose	70-100	mg/dl
3	Total Cholesterol	Less than 200	mg/dl
4	LDL	Less than 130	mg/dl
5	HDL	40 M, 50 F	mg/dl
6	Total Triglycerides	Less than 150	mg/dl

Blood samples were collected from the antecubital vein and placed in EDTA-containing tubes. The samples were stored at -80°C after centrifugation till the date of analysis. The collected blood samples were analyzed using targeted antibodies after performing ELISA. The results of ELISA were described and presented. Then, appropriate statistical methods were employed for the analysis of the obtained results.

3. RESULTS

The key findings indicated the anomalous function of AKT protein present in pancreatic β cells, as well as the disruption in PKC pathway that causes phosphorylation in alpha and beta cells of pancreas which results in diabetes and leads to heart attack. The aberrant changes in sugar test and lipid profile including Hb1Ac (9%), fasting blood glucose (250mg/dl), total cholesterol (342mg/dl), LDL (Less than 250mg/dl), HDL (49 F mg/dl), and total triglycerides (215mg/dl) causes serious discomfort for patients. To analyze the data collected from 30 patients admitted in the cardiology ward, an assessment proforma was built which included anthropometric measurements, physical activity level, dietary history, and blood tests for lab findings such as lipid profiles.

In normal human metabolism, a high glucose level stimulates insulin

production. During insulin resistance, beta cells produce insulin which is not used by cells. The cause of abnormality in this process is fat deposition in the adipose tissue or the destruction of LDL (see Figure 2).

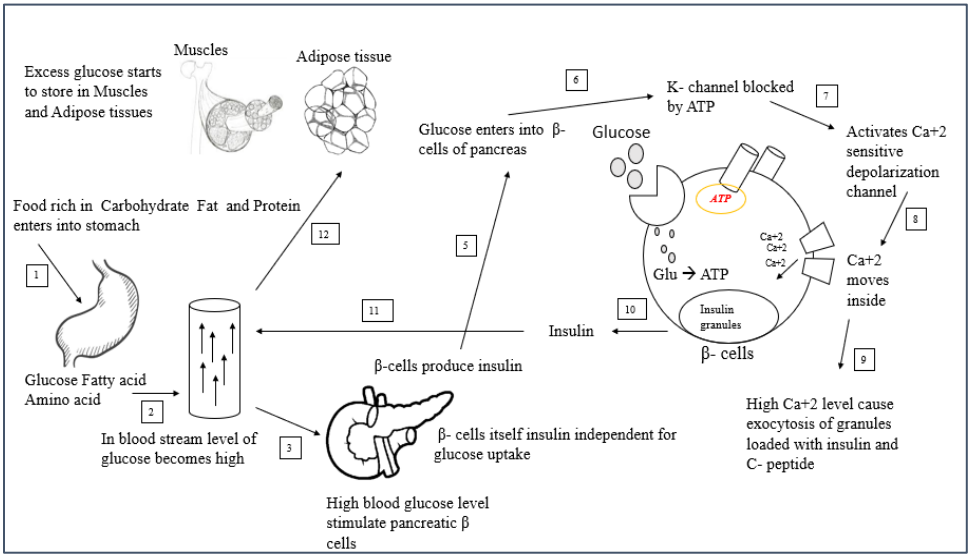

Figure 2. Diagram Shows the Activation of β-cells and its Function for Glucose

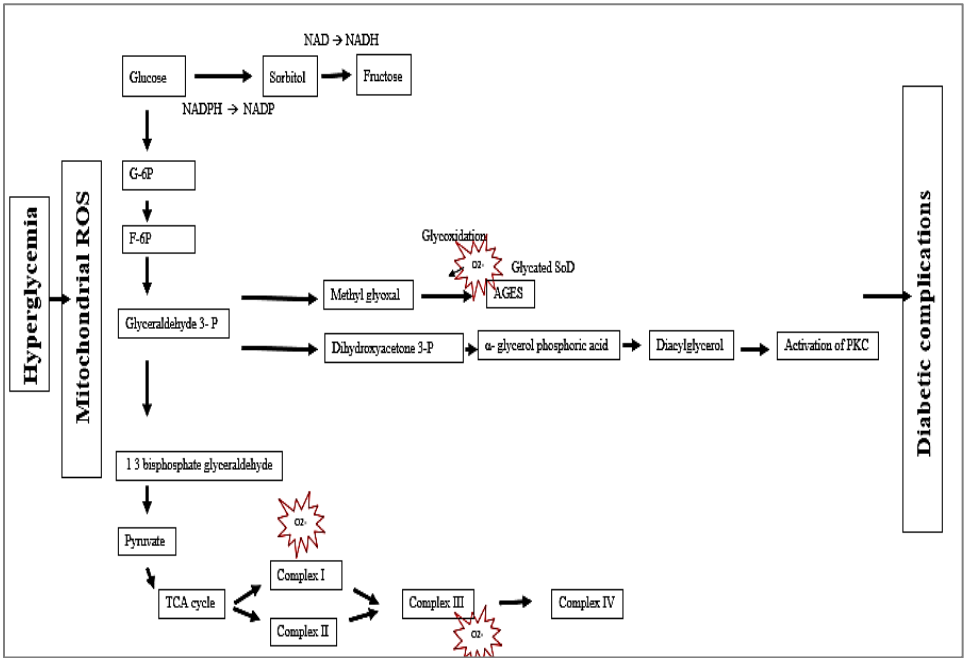

Figure 3. Diagram Shows How Hyperglycemia Effect 3 Pathways Including Polyol, PKC and AGEs Pathway

Figure 2 depicts a scenario where under normal circumstances, postprandial glucose levels in the bloodstream experience a surge, thereby activating the β-cells of pancreas which have the ability to produce insulin. Following the exhilaration of these β-cells, the level of insulin increases within the bloodstream, ultimately restoring glucose levels to their optimal range. Nevertheless, in instances where insulin production is insufficient to satisfy glucose requirements, glucose levels remain constant in the bloodstream [12-14].

In hyperglycemic state, a high level of glucose disturbs the normal metabolic functions. All these processes occur in the mitochondria of cells. The activation of oxidants is the primary factor which becomes the cause of protein kinase C (PKC) activation and the emergence of diabetic condition (see Figure 3).

Figure 3 illustrates that elevated hyperglycemia leads to a significant surge in the formation of oxidants or reactive oxygen species (ROS), emanating from the mitochondria. Notably, the deleterious effects of hyperglycemia are attributed to the activation of three primary pathways, namely the polyol pathway, protein kinase C (PKC) pathway, and the accumulation of advanced glycated end product (AGEs), which collectively contribute to the initiation of diabetes [15].

Initially, insulin attaches to beta units. Then, tyrosine kinase binds amino acids with it and starts phosphorylation. Insulin receptor cells are activated and in the presence of AKT (protein kinase B), glucose fuses inside the cells (see Figure 4).

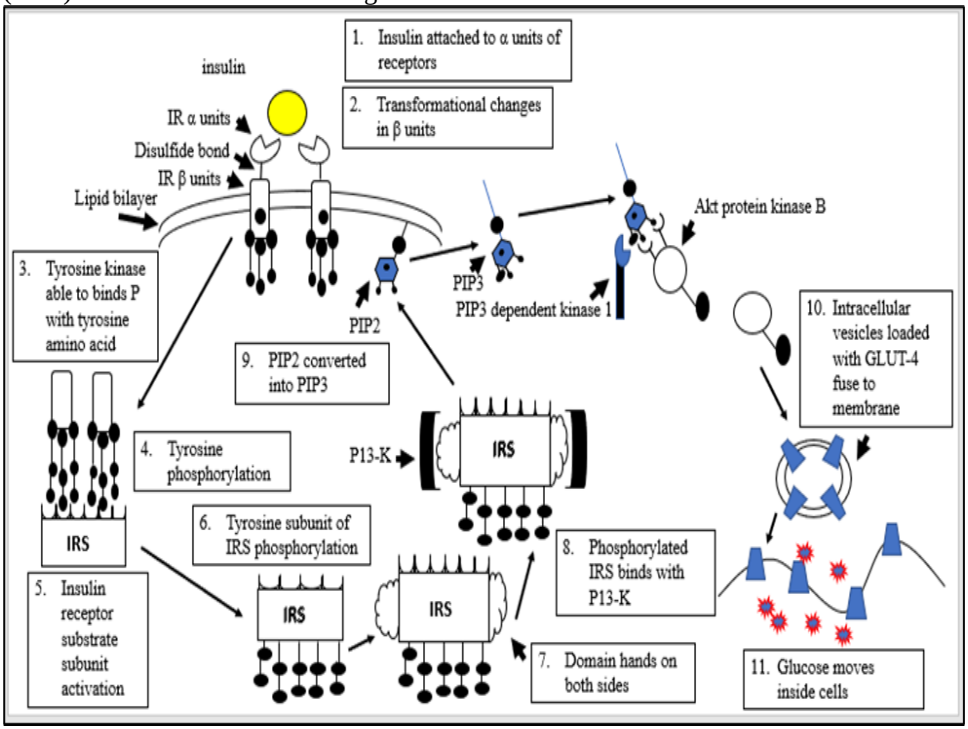

Figure 4. Diagram Shows How Insulin Play its Role that Glucose Available to Cell

Figure 4 depicts the binding of insulin to the α unit of insulin receptors, inducing the addition of the phosphate group in insulin β cells (phosphorylation). Subsequently, phosphorylation activates the receptor cells of insulin, resulting in the attachment of P13-K to a range of hands in each side. This crucial process stimulates the action of AKT protein kinase B, which serves as a pivotal player in facilitating glucose transfer into the cells.

3.1. Atherosclerosis

Atherosclerotic plaque formation is primarily attributed to the deterioration of low density lipoproteins (LDL), also known as bad fat. Atherosclerosis is a pathological condition characterized by the development of knotty or complex atherosclerotic plaques (clot), due to which arterial walls become stiffened and slandered [16]. The term ‘atherosclerosis’ comprises two Greek words, namely ‘atherosis’ and ‘sclerosis’. Atherosis refers to fat accumulation accompanied by many types of macrophages also known as kupffer cells, whereas the formation of fibrotic tissue is a sign of sclerosis. These tissues are composed of smooth/visceral muscle cells, areolar, and white blood cells (leukocyte) [17].

Although atherosclerosis or ‘hardening of walls’ is not a condition which emerges after lipoprotein deposition, it starts from the deterioration of the innermost layer of an organ which is called intima. It can result in increased number of lipid laden macrophages at the affected area and the formation of hard lipid plaques (atherosclerotic) [18]. The mechanism of atherosclerosis entails three primary steps, namely the emergence of seudonophilic lesion of fat, the development of thrombus, and the emergence of LDL (atherosclerotic clot deposition). A comprehensive understanding of the decomposition of LDL entails how it contributes to the formation of lipid plaque which necessitates a detailed explanation in atherosclerosis.

3.1.1. Fatty Strips Formation. To obtain a comprehensive understanding of the manner in which the oxidation of bad cholesterol becomes the cause of plaque formation, it is imperative to elucidate the global structural and morphological process associated with the formation of fatty plaque (atherosclerosis). The atherosclerotic activity encompasses a series of fundamental steps.

- Initially, when low density lipoprotein cholesterol (LDL-C) concentration increases in blood plasma, LDL-C enters endothelialium or fibroblast through a process known as endocytosis. As a result, blood plasma LDL increases to a crucial level and post-synaptic proteoglycans (decorin, biglycan, fibromodulin) augment. Since extracellular elements and LDL both have mutual affection and correlation, the latter becomes entrapped in the innermost wall of arteries which is an affected area. It becomes the cause to elevate the concentration and duration of the stay inside intima, ultimately resulting in direct degeneration of captured LDLs.
- Secondly, Ox-LDL works as an influencer or antigen for T-cells (T-lymphocytes) and consequently activates them. These cells produce lymphokines that start sending massages to endothelial smooth muscle cells and macrophages to proceed the next step.
- Thirdly, sticking molecules

production starts on leucocytes when endothelial cells start working or are altered. Adhesion or sticking molecules possess particular sensory receptors that are exclusively expressed on specific leukocytes, smooth muscle cells (involuntary), and endothelial cells. Transcription is performed on vascular endothelial surface when sticking or adhesive receptors start sending massages. Then, alpha and beta cells of pancreas activate its transcription factor NF by connecting proinflammatory lymphokines to their sensory receptors present on the endothelial surface. These sticking molecules or components play a vital role in cytokine formation and excretion, which further contribute to the mobilizing and discharge of WBC (leukocytes).

- Fourthly, after insertion into intima, phagocytes differentiate into macrophages. With the help of scavenger/hunter receptors, macrophages execute the accretion of Ox-LDL, which then converts to a yellowish foam like structure called lipid-laden macrophage. During monocytes to kupffer cells discrimination, all expression of these receptors is augmented by lymphokines and bad cholesterol. Phospholipids present on the surface of the Ox-LDL ligand instigate its binding to receptors, resulting in oxidation at two distinct sites. This process ultimately culminates in the generation of aldehydes. Lipid long fiber like strips are formed when yellow foam like structure of lipid-laden macrophages starts aggregating on the walls of arteries. Occasionally, a cytotoxic and dangerous compound secreted from the monocytes itself becomes the reason of LDL destruction and toxicity.

3.1.2. Genesis of Atheroma. The process of atheroma formation involves the secretion of short strings of amino acids, namely lymphokines, by endothelial cells. These factors, including interleukin 1 (IL-1) which is a lymphocyte activating factor and tumor necrosis factor or TNF, facilitate smooth/mural muscle cell relocation along with the formation of cell components present outside the cell. This is the reason behind the development of a fibrous cap like structure which consists of structural protein collagen, a fiber tissue, kupffer cells, and T. cells (a type of white blood cells).

3.1.3. Formation of Atherosclerosis Plaque/Clot. The factors mentioned above contribute to the development of a mature atherosclerotic plaque which can obstruct blood flow in arteries. Ox-LDL is a key player in the atherosclerotic process, being involved in various procedures, as well as the stimulation of lymphocytes, stimulation of the innermost layer of the cell known as endothelial cell and its abnormal functioning, stimulation of macrophages, up-regulation of adhesion molecules, production of lipid-laden cells, and procreation and relocation of mural cell [19, 20].

3.1.4. Dietary Administration to Control LDL Oxidation. In order to control the oxidation and glycation of LDL, it is imperative to adopt strategies that focus on nutrition. Certain sources of oxidized fat, such as fatty fish, immersion frying, and powdered/carpeted foods, should be avoided. Decomposed/rusted fish oils can also lead to the suppression of tochopherols (free radical scavengers) defense mechanism and secondary

cholesterol peroxides may also induce toxic effects. Moreover, global researches concluded that stressed oils may contribute to the progression of atherosclerosis. Dehydrated foods and deep-fried foods, which contain an abundant quantity of cholesterol oxides, have atherogenic effects and should be consumed in moderation.

3.1.5. Dietary Sources that Inhibit LDL Oxidation and Glycation. The consumption of certain dietary resources has been found to hinder the formation of bad cholesterol. Specifically, the consumption of vitamin E has visible positive effects in the action and usage of paraoxonase enzyme 1 in blood stream, thereby reducing oxidative stress and protecting lipids from oxidation. Previous research also established a mutual correlation between elevated levels of tochopherols (vitamin E) and reduced free radicals [21].

3.1.6. Polyphenols. They are the main free radical scavengers present in the daily food intake of human beings. These compounds work against both free radicals and inflammation. Herbs and spices used in food preparation and seasoning experience high concentrations of polyphenoles and flavonoids. These spices and herbs have very low calorie content in them so they are good for diabetic patients. Their benefit is high blood glucose level which elevates protein glycosylation without enzymes. However, literature suggests that an extract of certain seasonings is sometimes able to stop the genesis of AGEs.

Test tube experiments showed that about 50% ethanolic end product of certain seasonings can hinder the glycation of fructose arbitrate protein. Specifically, isolated end products of cinnamon and ground Jamaican pepper or allspice have been found to be useful to obstruct the process of glycation [22].

3.1.7. Histidine and Carnosine. These are well-known antioxidants produced in the liver, skeletal muscle, and brain. These compounds scavenge and destroy free radicals (antioxidant) and bind ionic minerals. The decomposition of LDL and glycation are consequences of elevated glucose levels in the blood. It may damage blood vessels and may also lead to CVD, stroke, and myocardial infarction. However, histidine and carnosine prevent from the degeneration of bad cholesterol and glycation. When diabetic mice intake histidine and carnosine by 1 g/l ratio for a period of 4 weeks, it has been found to significantly reduce their blood glucose and fibronectin levels, while also elevating their insulin level. These elements show different effects when the dose is different. Treatment with 1 g/l of these antioxidants remarkably increased the activity of glutathione peroxidase (GPx-1) which is an intracellular antioxidant enzyme. Moreover, glucose level is hindered in diabetic mice by the ingestion of histidine or carnosine [23].

4. DISCUSSION

4.1. Diet Planning of Diabetic Patients

Case Study: A 57-year old Kausar Bibi was admitted to the hospital with active complaint of B/L pedal edema, chest pain, and left lower limb numbness. She had a family history of diabetes. She had decreased appetite. Her body weight was 82 kg and her height was 5 feet and 6 inches. Her sleeping pattern was disturbed as well. She was a chain smoker. She was diagnosed with diabetes and peripheral arterial disease.

Medical Record (MR) Number = 23511259

Table 2. Abnormal Ranges of Laboratory Tests

Sr. No	Test Name	Results	Normal Ranges	Unit
1	Hb1Ac	9	4-5.6	%
2	Fasting Blood Glucose	250	70-100	mg/dl
3	Total Cholesterol	342	Less than 200	mg/dl
4	LDL	250	Less than 130	mg/dl
5	HDL	49	40 M, 50 F	mg/dl
6	Total Triglycerides	215	Less than 150	mg/dl

4.2. Anthropometric Assessment

- Weight= 82kg
- Height= 5 feet 6 inches
- BMI= 29.2kg/m^2
- Age= 57 years
- BMR= 1331.03 Kcal

4.3. Medical Nutrition Therapy

- Carbohydrates 45-55·/· (complex carbs)
- Protein 15-20·/·
- Fat 25-30·/· (7·/· saturated fat)
- Fiber 35 grams

Table 3. Diet Plan

Timing	Diet	Amount	Calories
6 AM (Pre-breakfast)	Fresh apple	1	60
8AM (Breakfast)	Egg Omelate	1	75
	Whole grain roti	1	80
10PM (Brunch)	Chicken stock	1 cup	120
1PM (Lunch)	Whole grain roti	1	80
	Curry chicken	1plate	120
	Salad	1cup	25
4PM (Snack)	Chicken kabab	2	120
6PM	Sandwich	1	120
8PM (Dinner)	Khichri	1 cup	205
10PM (Post-dinner)	Milk	1 glass	240

Total Calories: 1331 kcal

4.4. Conclusion

Oxidative stress and obesity have been linked with many modern disorders, as well as diabetes mellitus (DM), cardio vascular disease (CVD), and cancer. Globally, CVDs have become a crucial reason of mortality. These diseases are induced along with/due to inflammatory stress caused by oxidation. Low density lipoprotein (LDL) is oxidized/denatured and develops AGEs. Ox-LDL is the final stage that damages biological cell mechanisms while disrupting their normal actions, leading to disease development. Dietary oxidation is a major contributor to the formation of Ox-LDL and AGEs. These can be dispatched or managed with a balanced dietary intake and via the consumption of phytonutrients on a daily

basis. Insulin resistance starts due to cell inactivity and becomes a main factor or cause of diabetes/high blood glucose. Diabetes should only be managed by a balance diet containing low carbohydrates, moderate proteins, and modified fats. LDL oxidation/destruction affect the metabolic process by inhibiting or reducing many important enzyme activities necessary for glucose uptake.

CONFLICT OF INTEREST

The authors of the manuscript have no financial or non-financial conflict of interest in the subject matter or materials discussed in this manuscript.

DATA AVALIABILITY STATEMENT

The data associated with this study will be provided by the corresponding author upon request.

REFERENCES

1. World Health Organization. Global health estimates: Leading causes of death. *World Health* Organization Website. https://www.who.int/data/gho/data/themes/mortality-and-global-health-estimates/ghe-leading-causes-of-death. Accessed May 24, 2023.

2. Holvoet P, Harris TB, Tracy RP, et al. Association of high coronary heart disease risk status with circulating oxidized LDL in the well-functioning elderly: findings from the health, aging, and body composition study. arteriosclerosis, thrombosis, and vascular biology. *Arterioscler Thromb Vasc Biol*. 2023;23(8):1444–1448. https://doi.org/10.1161/01.ATV.0000080379.05071.22

3. American Diabetes Association. *Classification and diagnosis of diabetes:* standards of medical care in diabetes—2019. *Diabetes care. 2019;*42(supplement_1):S13–S28. https://doi.org/10.2337/dc19-S002

4. Tuleab SF. Glutathione, Vitamin C, Malonodialdehyde oxidized low-density lipoprotein and lipid profile levels in type 2 diabetic Iraqi Males. *Nahrain J Sci. 2016*;19(1):48–55. https://www.iasj.net/iasj/download/572be397f457c43f.

5. Reusch JE. Current concepts in insulin resistance, type 2 diabetes mellitus, and the metabolic syndrome. *Am J Cardiol*. 2002;90(5):19–26. https://doi.org/10.1016/S0002-9149(02)02555-9

6. Leahy JL. Pathogenesis of type 2 diabetes mellitus. *Arch Med Res*. 2005;36(3):197–209. https://doi.org/10.1016/j.arcmed.2005.01.003

Keane K, Cruzat VF, Carlessi R, De Bittencourt PI, Newsholme P. Molecular events linking oxidative stress and inflammation to insulin resistance and β-cell dysfunction. *Oxid Med Cell Longev*. 2015;2015:e181643. https://doi.org/10.1155/2015/181643

8. Czech MP. Insulin action and resistance in obesity and type 2 diabetes. *Nat Med*. 2017;23(7):804–814. https://www.nature.com/articles/nm.4350.

9. Almajwal AM, Alam I, Abulmeaty M, Razak S, Pawelec G, Alam W. Intake of dietary advanced glycation end products influences inflammatory markers, immune phenotypes, and antiradical capacity of healthy elderly

in a little-studied population. *Food Sci Nutr*. 2020;8(2):1046–1057. https://doi.org/10.1002/fsn3.1389

10. Chen M, Nagase M, Fujita T, Narumiya S, Masaki T, Sawamura T. Diabetes enhances lectin-like oxidized LDL receptor-1 (LOX-1) expression in the vascular endothelium: possible role of LOX-1 ligand and AGE. *Biochem Biophys Res Commun*. 2001;287(4):962–968. https://doi.org/10.1006/bbrc.2001.5674

11. Davies MJ, Aroda VR, Collins BS, Gabbay RA, Green J, Maruthur NM. Management of hyperglycemia in type 2 diabetes, 2022. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care*. 2022;45(11):2753–2786. https://doi.org/10.2337/dci22-0034 .

12. Cura AJ, Carruthers A. The role of monosaccharide transport proteins in carbohydrate assimilation, distribution, metabolism and homeostasis. *Compr Physiol*. 2012;2(2):863–914. https://doi.org/10.1002%2Fcphy.c110024

13. Ebert K, Ludwig M, Geillinger KE, Schoberth GC, Essenwanger J, Stolz J. Reassessment of GLUT7 and GLUT9 as putative fructose and glucose transporters. *J. Membr Biol*. 2017;250:171–182.

14. Kellett GL, Brot-Laroche E, Mace OJ, Leturque A. Sugar absorption in the intestine: the role of GLUT2. *Annu Rev Nutr*. 2008;28:35–54. https://doi.org/10.1146/annurev.nutr.28.061807.155518

15. Adil M, Waseem M, Haider AQ, Hussain N. Variations in genomic epidemiology and in-silico screening of potential phytochemicals to cure Monkeypox. *Adv Life Sci*. 2023;10(2):161–166.

16. Lee Y, Hsu C, Lin MH, Liu KS, Yin MC. Histidine and carnosine delay diabetic deterioration in mice and protect human low density lipoprotein against oxidation and glycation. *Euro J Pharm*. 2005;513(1-2):145–150. https://doi.org/10.1016/j.ejphar.2005.02.010

17. Rafieian-Kopaei M, Setorki M, Doudi M, Baradaran A, Nasri H. Atherosclerosis: process, indicators, risk factors and new hopes. *Int J Prev Med*. 2014;5(8):927–946.

18. Linton MF, Yancey PG, Davies SS, et al. *The role of lipids and lipoproteins in atherosclerosis.* South Dartmouth: 2019. https://www.ncbi.nlm.nih.gov/sites/books/NBK343489/

19. Bonora E, Formentini G, Calcaterra F, Lombardi S, Marini F, Zenari L. HOMA-estimated insulin resistance is an independent predictor of cardiovascular disease in type 2 diabetic subjects: prospective data from the Verona Diabetes Complications Study. *Diabetes Care*. 2002;25(7):1135–1141. https://doi.org/10.2337/diacare.25.7.1135 .

20. Manzoor MF, Arif Z, Kabir A, et al. Oxidative stress and metabolic diseases: relevance and therapeutic strategies. *Front Nutr*. 2022;9:e994309. https://doi.org/10.3389/fnut.2022.994309

21. Reaven PD, Herold DA, Barnett J, Edelman S. Effects of vitamin E on susceptibility of low-density

lipoprotein and low-density lipoprotein subfractions to oxidation and on protein glycation in NIDDM. *Diabetes Care*. 1995;18(6):807–816. https://doi.org/10.2337/diacare.18.6.807

22. Dearlove RP, Greenspan P, Hartle DK, Swanson RB, Hargrove JL. Inhibition of protein glycation by extracts of culinary herbs and spices. *J Med Food*. 2008;11(2):275–281. https://doi.org/10.1089/jmf.2007.536

23. Lee YT, Hsu CC, Lin M, Liu KS, Yin MC. Histidine and carnosine delay diabetic deterioration in mice and protect human low density lipoprotein against oxidation and glycation. *Euro J Pharm*. 2005;513(1-2):145–150. https://doi.org/10.1016/j.ejphar.2005.02.010.