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Evaluation the Risk of Atherosclerosis Among Some Iraqi Hyperlipidemic Patients Taking Atorvastatin

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Abstract

Background: Hyperlipidemia is a family of disorders that are characterized by abnormally high levels of lipids in the blood. While fats play a vital role in the body's metabolic processes, high blood levels increase the risk of atherosclerosis and cardiovascular diseases, especially coronary heart disease (CHD). This research aims to provide an investigation of hyperlipidemia and will focus on the atherogenic index of plasma (AIP) and The Castelli's risk indexes (CRI-I & CRI-II) which are strong markers to predict the risk of atherosclerosis and coronary heart disease.

Methodology: In this cross-sectional study, one hundred forty-nine Iraqi male and female patients with primary hyperlipidemia of the age of 28 to 85 years, who were treated with atorvastatin 40mg for at least 6 months were recruited. Lipid profile and liver functions were assessed, and the AIP and CRI-I & CRI-II were calculated to predict the risk of atherosclerosis and coronary heart disease.

Results: The study's finding shows there are 42 patients (28.2%) with good response to the statin therapy (atorvastatin 40 mg), about 35% of studied patients with a moderate response and about 39% of patients had poor or non-response after at least 6 months of the treatment. Additionally, there are 17 patients (11.4%) with a low risk of IHD, 3.4% with a moderate risk, and 85% of studied patients had a high risk of IHD according to the results of AIP. According to CRI-I and CRI-II there are 68 and 118 patients at low risk and 81, 31 patients at high risk to IHD respectively. Significant differences were observed in the levels of TC, BMI, and AIP between the age groups of the studied patients. Moreover, there are significant differences in the levels of TC, and AST regarding to the duration of treatment groups of the studied patients.

Conclusion: The study highlights varying responses to atorvastatin, with 39% showing poor or no response. AIP results indicate that 85% of patients are still at high IHD risk, supported by CRI-I and CRI-II assessments.

تقييم خطر تصلب الشرايين بين بعض المرضى العراقيين المصابين بفرط شحميات الدم الذين يتناولون الأتورفاستاتين

خالد قاسم محمد، مازن حامد عودة، سوزان جبير

الخلاصة

المقدمة

فرط شحميات الدم هو مجموعة من الاضطرابات التي تتميز بارتفاع غير طبيعي في مستويات الدهون في الدم. وعلى الرغم من أن الدهون تلعب دورًا حيويًا في العمليات الأيضية داخل الجسم، إلا أن ارتفاع مستوياتها في الدم يزيد من خطر الإصابة بتصلب الشرايين وأمراض القلب والأوعية الدموية، وخاصة مرض الشريان التاجي .(CHD) يهدف هذا البحث إلى دراسة فرط شحميات الدم مع التركيز على مؤشر تصلب الشرايين في البلازما (AIP) ومؤشري كاستيلي للمخاطر(CRI-I وCRI-II)، اللذين يُعتبران مؤشرات قوية للتنبؤ بخطر الإصابة بتصلب الشرايين ومرض القلب التاجي.

العينات وطرق العمل

في هذه الدراسة المقطعية، تم تجنيد 149 مريضًا ومريضة عراقيين يعانون من فرط شحميات الدم الأولي، تتراوح أعمارهم بين 28 و85 عامًا، وخضعوا للعلاج بعقار أتورفاستاتين بجرعة 40 ملغ لمدة لا تقل عن 6 أشهر. تم تقييم ملف الدهون ووظائف الكبد، كما تم حساب مؤشرات AIP و CRI-Iو CRI-IIللتنبؤ بخطر تصلب الشرايين ومرض القلب التاجي.

النتائج

أظهرت نتائج الدراسة أن 42 مريضًا (28.2%) استجابوا بشكل جيد لعلاج الستاتين (أتورفاستاتين 40 ملغ)، في حين كان لدى حوالي 35% استجابة معتدلة، و39% لم يكن لديهم استجابة كافية أو لم يستجيبوا للعلاج بعد ستة أشهر على الأقل. بالإضافة إلى ذلك، تبين أن 17 مريضًا (11.4%) لديهم خطر منخفض للإصابة بمرض القلب الإقفاري(IHD) ، و3.4% لديهم خطر معتدل، في حين أن 85% من المرضى المشمولين بالدراسة كانوا معرضين لخطر مرتفع وفقًا لنتائج مؤشر .AIP ووفقًا لمؤشري-CRI IوCRI-II، كان هناك 68 و118 مريضًا على التوالي في فئة الخطر المنخفض، و81 و31 مريضًا على التوالي في فئة الخطر المرتفع للإصابة بمرض القلب الإقفاري. كما لوحظت فروق ذات دلالة إحصائية في مستويات الكوليسترول الكلي(TC) ، ومؤشر كتلة الجسم(BMI) ، ومؤشر AIP بين الفئات العمرية للمرضى. علاوة على ذلك، وُجدت فروق ذات دلالة إحصائية في مستويات الكوليسترول الكلي (TC) وإنزيم AST بين مجموعات المرضى وفقًا لمدة العلاج.

الاستنتاج

تسلط الدراسة الضوء على التباين في استجابة المرضى لعقار أتورفاستاتين، حيث أظهر 39% منهم استجابة ضعيفة أو معدومة. كما تشير نتائج مؤشر AIP إلى أن 85% من المرضى لا يزالون معرضين لخطر مرتفع للإصابة بمرض القلب الإقفاري، وهو ما تؤكده أيضًا تقييمات مؤشري CRI-I و.CRI-II

1. Background

Hyperlipidemia is recognized as a significant risk factor for the development of cardiovascular diseases (CVDs) (Alloubani et al., 2021). It involves an elevated level of one or more plasma lipids, such as triglycerides, cholesterol, cholesterol esters, and phospholipids, or plasma lipoproteins, including very low-density lipoprotein (VLDL) and low-density lipoprotein (LDL), along with a decrease in high-density lipoprotein (HDL) levels (Sheeba and Gandhimathi, 2021). Elevated cholesterol (hypercholesterolemia) and triglyceride levels (hypertriglyceridemia) are primary contributors to atherosclerosis, a condition closely associated with ischemic heart disease (IHD) (Shao et al., 2020). Atherosclerosis is characterized by the hardening of arteries caused by cholesterol buildup within the arterial walls, leading to their narrowing. Hyperlipidemia contributes to the progression of atherosclerosis and increases the risk of related conditions, such as coronary, cerebrovascular, and peripheral vascular diseases (AL-Ezzy and Hameed, 2021). Hyperlipidemia is associated with heightened oxidative stress, resulting in the excessive production of oxygen free radicals. These radicals can cause oxidative modifications in low-density lipoproteins (LDL), which play a crucial role in the onset and progression of atherosclerosis and related CVD (Pappan et al., 2024). Statins are a group of medications that inhibit the enzyme 3-hydroxy-3-methylglutaryl-CoA reductase, thereby reducing the production of cholesterol in the body. They are the most commonly prescribed drugs for lowering lipid levels and are widely used for both the prevention and management of CVDs (Zhou and Liao, 2009, Mills et al., 2011) which remain the leading cause of death globally (Mc Namara et al., 2019). The development of CVDs is influenced by several established risk factors, including diabetes, elevated blood glucose levels, lack of physical activity, smoking, low levels of HDL cholesterol, and increased levels of LDL cholesterol (Sun et al., 2015). Therefore, effectively managing hypertension and dyslipidemia is essential for reducing the risks associated with CVD. Today, satins are the most effective oral medications for preventing and treating cardiovascular events caused by hypercholesterolemia (Ramkumar et al., 2016). Clinical trials have demonstrated that statins not only reduce LDL cholesterol and triglyceride (TG) levels (Ramkumar et al., 2016), but also decrease the morbidity and mortality linked to coronary heart disease, cerebrovascular disease, and peripheral arterial disease (Mills et al., 2011).The atherogenic index of plasma (AIP) serves as a reliable indicator for assessing the risk of atherosclerosis and coronary heart disease (Wu et al., 2021). It represents the balance between protective and atherogenic lipoproteins and correlates with the size of lipoprotein particles involved in atherogenesis (Niroumand et al.). AIP is calculated according to the formula, log(TG/HDL-C) (Askin and Tanriverdi, 2023). Castelli's risk indexes (CRI-I and CRI-II), also known as cardiac risk indexes, are two lipid ratios associated with CVD risk. CRI-I represents the ratio of total cholesterol (TC) to HDL-C, while CRI-II is the ratio of LDL-C to HDL-C (Olamoyegun et al., 2016). These indexes were introduced by William Castelli in the late 20th century (Abid et al., 2021), and subsequent studies have confirmed their strong positive correlation with CVD risk (Gómez-Álvarez et al., 2020, Igharo et al., 2020). CRI-I has been specifically shown to reflect the formation of coronary plaques and the thickness of the carotid artery intima-media in young adults(Nair et al., 2009, Frontini et al., 2007). This research aims to evaluate the risk of atherosclerosis and CVD among some Iraqi hyperlipidemic patients on atorvastatin treatment.

2. Materials and Methods

2.1. Study subjects

This research was conducted as a cross-sectional observational study at Imam Al-Hussain Medical City and the Kerbala Center for Cardiac Diseases and Surgery in Karbala, spanning from November 2023 to April 2024. The study received approval from the Scientific and Ethical Committee of the College of Pharmacy, University of Kerbela. Informed consent was obtained from all participants after explaining the purpose and details of the study. The study included 149 participants (80 males and 69 females), aged between 28 to 85 years, who had been receiving a daily oral dose of 40 mg atorvastatin as monotherapy for hyperlipidemia for a minimum of six months. During blood sample collection, participants were asked about any additional medications that could potentially influence atorvastatin metabolism.

Data were gathered from both medical records and direct interviews with participants. The collected information included age, weight, height, smoking habits, treatment duration, adverse drug reactions, other medical conditions, and concurrent medications.

Five milliliters of venous blood were drawn from the participants, and was kept in gel tube, centrifuged to get the serum, which was then used for the biochemical analysis. These parameters included lipid profile (HDL, LDL, TC, and TG levels) which performed by The cobas c 311 analyzer, developed by Roche Diagnostics, HDL cholesterol is measured using a homogeneous enzymatic colorimetric assay, Roche's HDL-C Gen.4 reagent is utilized for this analysis. The determination of LDL cholesterol is performed using a direct homogeneous assay, Roche's LDL-C Gen.3 reagent is utilized for this analysis, an enzymatic colorimetric method for total cholesterol (TC) determination Roche's Cholesterol Gen.2 reagent is specifically designed for this purpose and triglyceride levels (TG) measure. liver function tests which involve ALT level which is determined using the International Federation of Clinical Chemistry (IFCC) recommended method without pyridoxal phosphate. This kinetic assay measures the rate of NADH oxidation, which is directly proportional to ALT activity. Roche's ALTL reagent is employed for this test. Similar to ALT, AST activity is measured via the IFCC method without pyridoxal phosphate. The assay monitors the decrease in NADH absorbance, reflecting AST activity in the sample. The ASTL reagent from Roche is used for this purpose. Total bilirubin levels are measured using a colorimetric diazo method. In acidic conditions, bilirubin reacts with a diazo reagent to form azobilirubin, a colored compound. The intensity of the color is proportional to the total bilirubin concentration. Roche provides the BIL-T Gen.3 reagents for total bilirubin measurements, and random blood sugar RBS.

2.2. Statistical Evaluation

Statistical analysis was performed using IBM SPSS software, version 26. The data were entered into a computerized database to identify and address any errors or inconsistencies, as well as to organize, process, and analyze the information. Scale variables were presented as mean values with standard error of the mean (SEM), while categorical variables were reported as frequencies and percentages. A parametric test was used due to the normal distribution of the scale variables. One-way analysis of variance (ANOVA) was applied to compare means across more than two groups, with statistical significance $P \leq 0.05$.

3. Results

A total of 149 Iraqi participants, both male and female, with primary hyperlipidemia were included in this study. Their demographic details are outlined in Table1. Among the participants, 42 patients (28.2%) showed a good response to statin therapy (40 mg atorvastatin). Approximately 35% had a moderate response, while about 39% exhibited poor or no response. Table 1 also shows that 17 patients (11.4%) were classified as having a low risk of ischemic heart disease (IHD), 3.4% had a moderate risk, and 85% had a high risk of IHD based on AIP results. Regarding CRI-1, about 46% of patients were classified as low risk, while 54% were considered at high risk for CVD and atherosclerosis. For CRI-2, 80% of the participants were at low risk, and approximately 20% were at high risk for CVD and atherosclerosis.

Table1: The Demographic and Atherogenic Characteristics of the Hyperlipidemia Patients.

Variable		N	Percent
Gender	Male	80	53.7
	Female	69	46.3
Age	25-45	25	16.8
	46-65	95	63.8
	66-85	29	19.5
BMI	Under weight	1	0.7
	Normal	32	21.5
	Over weight	88	59.1
	Obese	27	18.1
Duration of treatment (months)	6-12	112	75.2
	13-24	25	16.8
	25-36	6	4.0
	37-48	6	4.0
Smoking	No smoke	100	67.1
	Smoker	49	32.9
Response (LDL level)	<50 Good	42	28.2
	51-100 Moderate	52	34.9
	>100 None	55	36.9
AIP	<0.11	17	11.4
	0.11-0.21	5	3.4
	>0.21	127	85.2
CRI-I	<3.5	68	45.6
	>3.5	81	54.4
CRI-II	<3	118	79.2
	>3	31	20.8
BMI: body mass index, AIP: Atherogenic Index of Plasma, CRI-1: Castelli's risk indexe-1, CRI-2**:** Castelli's risk indexe-2			

Table2 presents the mean levels of laboratory biomarkers in the study participants, categorized by age. Significant differences were observed in body mass index (BMI) between groups B and A, with a p-value of 0.014. Additionally, TC levels showed a significant difference between groups C and B, with a p-value of 0.036. A significant variation in AIP results was found between groups A vs. C and B vs. C, with p-values of 0.048 and 0.05, respectively. Furthermore, total bilirubin levels showed significant differences between groups B vs. A and C vs. A, with p-values of 0.034 and 0.042, respectively. Lastly, CRI-1 results revealed significant differences between groups A vs. C and B vs. C, with p-values of 0.034 and 0.032, respectively.

Table2: The Laboratory Biomarkers in the Hyperlipidemia Patients Categorized by Age

Parameter	A:25-45 years (n=25)	B:46-65 years (n=95)	C:66-85 years(n=29)	MC	P value
BMI	26.25±0.67	28.32±0.41	26.86±0.47	B vs A	0.014
SBP	129.60±4.93	134.01±1.86	135.45±3.51	NS	0.512
DBP	81.36±2.25	83.72±1.08	82.90±2.50	NS	0.646
RBS	149.32±23.50	139.74±5.66	154.48±15.22	NS	0.603
LDL	91.40±8.49	89.78±4.92	74.34±8.79	NS	0.268
HDL	43.20±3.46	46.15±1.72	50.10±5.51	NS	0.441
VLDL	29.52±3.45	28.70±1.47	23.20±2.06	NS	0.160
TC	160.44±10.78	163.14±5.12	140.28±9.60	C vs B	0.036
TG	147.60±17.28	143.55±7.38	116.03±10.32	NS	0.160
ALT	22.28±2.97	20.60±0.98	19.77±1.57	NS	0.669
AST	51.00±24.81	32.38±4.79	33.66±6.61	NS	0.434
TBL	0.820±0.14	0.544±0.05	0.500±0.08	B vs A C vs A	0.034 0.042
AIP	0.49±0.049	0.46±0.026	0.35±0.044	A vs C B vs C	0.048 0.050
CRI-1	4.20±0.324	3.83±0.151	3.15±0.250	A vs C B vs C	0.034 0.032
CRI-2	2.27±0.261	2.11±0.126	1.61±0.231	NS	0.105

BMI stands for body mass index, SBP refers to systolic blood pressure, DBP is diastolic blood pressure, RBS indicates random blood sugar, LDL represents low-density lipoprotein, HDL denotes high-density lipoprotein, VLDL refers to very low-density lipoprotein, TC stands for total cholesterol, TG indicates triglycerides, ALT represents alanine transaminase, AST refers to aspartate transaminase, TBL denotes total bilirubin, AIP for The Atherogenic Index of Plasma, and CRI-1 and CRI-2 for The Castelli's risk indexes (I & II)

Table3 presents the mean levels of laboratory biomarkers in the study participants, categorized by treatment duration. Significant differences were observed in total cholesterol (TC) levels between groups C and B, as well as in AST levels between groups C and A, and C and B.

Table3: Description of the Laboratory Biomarkers of the Studied Patients According to Duration of Treatment

Parameter	A-6-12 months (n=112)	B- 13-24 months (n=25)	C-25-36 months (n=6)	D-37-48 months (n=6)	MC	P value
BMI	27.61±0.35	28.36±0.922	25.87±1.09	28.26±0.61	NS	0.505
SBP	132.01±1.85	140.16±3.72	135.00±6.70	133.33±8.79	NS	0.310
DBP	82.76±0.97	84.56±2.50	85.83±4.90	82.17±8.83	NS	0.826
RBS	143.53±7.09	143.80±14.35	161.83±43.14	141.17±11.95	NS	0.949
LDL	84.21±3.97	89.13±12.59	120.86±22.71	97.60±21.08	NS	0.280
HDL	46.07±2.02	48.32±3.29	45.33±4.90	46.16±4.83	NS	0.965
VLDL	28.90±1.43	24.69±2.66	25.96±3.35	21.40±1.83	NS	0.383
TC	159.71±4.42	145.80±12.87	192.33±26.19	148.50±22.70	C vs B	0.047
TG	144.50±7.16	123.48±13.32	129.83±16.76	107.00±9.18	NS	0.383
ALT	20.52±0.86	19.58±1.71	35.83±10.33	14.06±1.46	NS	0.669
AST	29.57±2.21	44.04±17.20	130.33±102.94	22.06±2.87	C vs A C vs B C vs D	0.001 0.003 0.003
TBL	0.596±0.05	0.504±0.09	0.700±0.11	0.533±0.55	NS	0.851
AIP	0.47±0.025	0.37±0.04	0.45±0.77	0.37±0.06	NS	0.300
CRI-1	3.83±0.133	3.28±0.388	4.26±0.476	3.29±0.402	NS	0.258
CRI-2	2.09±0.106	1.75±0.361	2.64±0.440	1.79±0.350	NS	0.385

BMI stands for body mass index, SBP refers to systolic blood pressure, DBP is diastolic blood pressure, RBS indicates random blood sugar, LDL represents low-density lipoprotein, HDL denotes high-density lipoprotein, VLDL refers to very low-density lipoprotein, TC stands for total cholesterol, TG indicates triglycerides, ALT represents alanine transaminase, AST refers to aspartate transaminase, TBL denotes total bilirubin, AIP for The Atherogenic Index of Plasma, and CRI-1 and CRI-2 for The Castelli's risk indexes (I & II)

Table4 shows the correlation matrix for the relation of AIP on some related parameters under the study. The relation between TG and AIP is 0.745 with a P-value of 0.001.

Table4: Correlation Matrix for the Relation of AIP with Some Related Parameters Under the Study

Parameter	Status	AIP	SBP	LDL	TG
AIP	Correlation	1	0.041	0.618	0.745**
	p Value		0.618	0.153	0.001
SBP	Correlation	0.041	1	-0.106	0.057
	P value	0.618		0.200	0.492
LDL	Correlation	0.153	-0.106	1	0.134
	P value	0.062	0.200		0.103
TG	Correlation	0.745**	0.001	0.134	1
	P value	0.001	0.057	0.103	

4. Discussion

This study aimed to evaluate hyperlipidemia as a risk factor for atherosclerosis among the Iraqi hyperlipidemic patients taking atorvastatin. A total of 149 Iraqi participants, both male and female, with primary hyperlipidemia were included in this study. According to the guidelines for the management of dyslipidemia (European Society of Cardiology/European Atherosclerosis Society, ESC/EAS) (Mach et al., 2020) 28% of the patients showed a good response to statin therapy with LDL levels below 50 mg/dL. Approximately 35% had a moderate response, with LDL levels ranging from 51 to 100 mg/dL, while about 39% exhibited poor or no response, with LDL levels exceeding 100 mg/dL after at least six months of treatment. On evaluation of lipid ratios in the current study, AIP was significantly high in about 85% of studied patients which indicate high risk to IHD and atherosclerosis. AIP is a ratio calculated as

(log TG/HDL-C). Studies have shown an inverse relationship between TG and HDL-C and that the ratio of TG to HDL-C is a strong predictor of infarction (Sami Khaza, 2013). AIP is being used by some practitioners as a significant predictor of atherosclerosis. It has been suggested that AIP values of less than 0.1 are associated with low, 0.1 to 0.21 with medium and above 0.21 with high cardiovascular risk (Sadeghi et al., 2021). CRI is based on three important lipid profile parameters i.e. TC, LDL-C and HDL-C. CRI-I calculated as the ratio of (TC/HDL-C) and CRI-II as (LDL-C/HDL-C) (Yıldız et al., 2016). In about 54% of our patients, CRI-I was greater than 3.5, which represents the upper normal limit (Subia Jamil and Afshan Siddiq, 2012). This level of CRI-I associated with coronary plaques formation and increase risk to IHD. In our study, CRI-II was also found to be above the upper limit for normal range (>3) (Subia Jamil and Afshan Siddiq, 2012) in 21% of the studied patients. In PROCAM study, it was observed that subjects with LDL-C/HDL-C greater than 5 had six times higher rate of coronary events (Bhardwaj et al., 2013).Dyslipidemias is characterized by lipid circulatory disorders, including high levels of LDL-C, elevated triglycerides, high levels of TC, and low levels of HDL-C (Kopin and Lowenstein, 2017). LDL carries about 60–70% serum cholesterol (DiPiro et al., 2014) and transports the liver's cholesterol to the peripheral tissues. A high level of LDL-C is harmful because it can build up to initiate the formation of atherosclerotic plaques on the arterial walls (Elshourbagy et al., 2014). Atherosclerosis develops when the endothelial layer of blood vessels is damaged by factors such as hypertension, smoking, diabetes, and high LDL-C levels (Frąk et al., 2022). This damage compromises the integrity of the arterial wall, making it more permeable and allowing LDL particles to accumulate in the subendothelial space (Khatana et al., 2020). Once trapped by proteoglycans in the extracellular matrix, these LDL particles undergo oxidative changes due to reactive oxygen species (ROS) and enzymes like lipoxygenase, Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, and myeloperoxidase (Gianazza et al., 2021). The oxidation of LDL makes it highly reactive and toxic to cells, initiating a strong immune response. When oxidized LDL (oxLDL) accumulates in the arterial wall, the immune system perceives it as a harmful substance. In response, endothelial cells produce adhesion molecules such as vascular cell adhesion molecule 1 and intercellular adhesion molecule 1 , which facilitate the recruitment of white blood cells, particularly monocytes, to the affected area(Razeghian-Jahromi et al., 2022). Once monocytes infiltrate the arterial wall, they transform into macrophages that engulf oxLDL through specialized scavenger receptors like SR-A and CD36 (Lee and Choi, 2020). Unlike normal LDL uptake, this process lacks regulation, leading to continuous lipid accumulation within macrophages. As a result, these lipid-filled macrophages become foam cells, a key feature of early atherosclerotic plaques. Foam cells contribute to inflammation by releasing cytokines such as tumor necrosis factor-alpha , interleukin-1 beta , and monocyte chemoattractant protein-1 (Chistiakov et al., 2017). This inflammatory response further attracts immune cells and promotes additional LDL retention, accelerating plaque development. As the plaque grows, smooth muscle cells, influenced by growth factors like platelet-derived growth factor, migrate to the site and produce extracellular matrix proteins such as collagen, forming a fibrous cap over the lipid core to provide stability. However, persistent inflammation and mechanical stress can weaken this fibrous cap, making it prone to rupture(Jansen et al., 2024). If the cap breaks, the exposed thrombogenic material interacts with circulating blood, triggering platelet activation and the formation of a blood clot (thrombus). This can obstruct blood flow, leading to severe cardiovascular events such as a heart attack or stroke (Alkarithi et al., 2021). Large randomized trials have shown that lowering LDL-C with 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors

("statins") reduces coronary mortality and morbidity in some high-risk patients (Feingold, 2024).In this study, group C (ages 66–85 years) exhibited significantly lower TC levels and a reduced risk of IHD and atherosclerosis, as indicated by AIP and CRI-I results, compared to the younger groups (Table 2 and Table 3). This can be attributed to several physiological, pharmacological, and behavioral factors such as variations in drug metabolism, particularly in the liver, play a significant role in the effectiveness of atorvastatin. Aging can slow liver metabolism, which is responsible for processing the drug. As a result, higher circulating levels of atorvastatin may enhance its cholesterol-lowering effects(Hirota et al., 2020). Lifestyle factors also influence cholesterol management. Older adults tend to adhere more consistently to prescribed medications and lifestyle modifications, such as maintaining a healthier diet, which contributes to more effective cholesterol control. Additionally, they are more likely to attend regular follow-up appointments with healthcare providers, ensuring continuous monitoring and better management of their cholesterol levels. In contrast, younger individuals with high cholesterol may be less consistent in adopting lifestyle changes, such as improving their diet or increasing physical activity, as they often perceive that they have more time to address their health concerns. Regarding the duration of treatment, the results in (Table 3) indicates that group C, with a treatment duration of 25–36 months, shows significantly higher total cholesterol (TC) levels compared to group B, whose treatment duration ranges from 13–24 months. This difference may be attributed to factors such as reduced adherence to treatment, lifestyle influences, disease progression, or inadequate dosing. Group C also exhibits significantly higher levels of AST compared to the other groups. This may be explained by the mechanism of atorvastatin, which inhibits HMG-CoA reductase in the liver to reduce cholesterol production (Jiang et al., 2018). Over time, this process could slightly strain liver cells, potentially causing mild and chronic elevations in liver enzymes for some patients. Additionally, prolonged exposure to the drug might result in minor liver cell injury or increased cell turnover, when hepatocytes are injured, the breakdown of both the plasma membrane and mitochondrial membranes causes the release of intracellular enzymes like AST into the blood (Contreras-Zentella and Hernández-Muñoz, 2016). This happens due to structural damage, oxidative stress, inflammation, and impaired energy production, all of which compromise the cell's ability to maintain its integrity and lead to the leakage of AST (Herrick et al., 2016, Ziolkowska et al., 2021). Prolonged use of atorvastatin may lead to mild muscle injury in certain individuals, a condition known as statin-induced myopathy. Because AST is present in muscle tissue as well as the liver, muscle damage could be a contributing factor to increased AST levels (Taha et al., 2014). According to the correlation between AIP and the other parameters, as demonstrated in (Table 4), there is a strong direct correlation between AIP and TG; as TG levels increase AIP levels also rise. This elevation in AIP is associated with a higher risk of IHD (Kim et al., 2021).

5. Conclusion

The study reveals variability in the patient's response to atorvastatin (40 mg) with only one third of patients showing a good response, while a significant portion exhibited moderate or poor/non-response. The AIP results indicate that the majority of patients are at high risk of IHD, with only a small fraction at low or moderate risk. Risk assessment using CRI-I and CRI-II further supports these findings, showing a considerable number of the patients at high risk. Additionally, significant differences in TC, BMI, and AIP levels were observed across different age groups, suggesting that age may influence lipid profile and cardiovascular risk.

References

ABID, H., ABID, Z. & ABID, S. 2021. Atherogenic indices in clinical practice and biomedical research: a short review. *Baghdad Journal of Biochemistry and Applied Biological Sciences,* 2**,** 60-70.

AL-EZZY, A. I. A. & HAMEED, M. S. 2021. The physiological Aspects of Hyperlipidemia in health and Disease.

ALKARITHI, G., DUVAL, C., SHI, Y., MACRAE, F. L. & ARIËNS, R. A. 2021. Thrombus structural composition in cardiovascular disease. *Arteriosclerosis, thrombosis, and vascular biology,* 41**,** 2370-2383.

ALLOUBANI, A., NIMER, R. & SAMARA, R. 2021. Relationship between hyperlipidemia, cardiovascular disease and stroke: a systematic review. *Current Cardiology Reviews,* 17.

ASKIN, L. & TANRIVERDI, O. 2023. Is the atherogenic index of plasma (AIP) a Cardiovascular Disease marker. *Cor et Vasa,* 65**,** 100-3.

BHARDWAJ, S., BHATTACHARJEE, J., BHATNAGAR, M., TYAGI, S. & DELHI, N. 2013. Atherogenic index of plasma, castelli risk index and atherogenic coefficient-new parameters in assessing cardiovascular risk. *Int J Pharm Biol Sci,* 3**,** 359-64.

CHISTIAKOV, D. A., MELNICHENKO, A. A., MYASOEDOVA, V. A., GRECHKO, A. V. & OREKHOV, A. N. 2017. Mechanisms of foam cell formation in atherosclerosis. *Journal of molecular medicine,* 95**,** 1153-1165.

CONTRERAS-ZENTELLA, M. L. & HERNÁNDEZ-MUÑOZ, R. 2016. Is liver enzyme release really associated with cell necrosis induced by oxidant stress? *Oxidative medicine and cellular longevity,* 2016**,** 3529149.

DIPIRO, J. T., TALBERT, R. L., YEE, G. C., MATZKE, G. R., WELLS, B. G. & POSEY, L. M. 2014. Pharmacotherapy: a pathophysiologic approach.

ELSHOURBAGY, N. A., MEYERS, H. V. & ABDEL-MEGUID, S. S. 2014. Cholesterol: the good, the bad, and the ugly-therapeutic targets for the treatment of dyslipidemia. *Medical Principles and Practice,* 23**,** 99-111.

FEINGOLD, K. R. 2024. Cholesterol lowering drugs. *Endotext [Internet]*.

FRĄK, W., WOJTASIŃSKA, A., LISIŃSKA, W., MŁYNARSKA, E., FRANCZYK, B. & RYSZ, J. 2022. Pathophysiology of cardiovascular diseases: new insights into molecular mechanisms of atherosclerosis, arterial hypertension, and coronary artery disease. *Biomedicines,* 10**,** 1938.

FRONTINI, M. G., SRINIVASAN, S. R., XU, J.-H., TANG, R., BOND, M. G. & BERENSON, G. 2007. Utility of non–high-density lipoprotein cholesterol versus other lipoprotein measures in detecting subclinical atherosclerosis in young adults (the Bogalusa heart study). *The American journal of cardiology,* 100**,** 64-68.

GIANAZZA, E., BRIOSCHI, M., MARTINEZ FERNANDEZ, A., CASALNUOVO, F., ALTOMARE, A., ALDINI, G. & BANFI, C. 2021. Lipid peroxidation in atherosclerotic cardiovascular diseases. *Antioxidants & redox signaling,* 34**,** 49-98.

GÓMEZ-ÁLVAREZ, E., VERDEJO, J., OCAMPO, S., PONTE-NEGRETTI, C. I., RUÍZ, E. & RÍOS, M. M. 2020. The CNIC-polypill improves atherogenic dyslipidemia markers in patients at high risk or with cardiovascular disease: results from a real-world setting in Mexico. *IJC Heart & Vasculature,* 29**,** 100545.

HERRICK, C., BAHRAINY, S. & GILL, E. A. 2016. Statins and the liver. *Endocrinology and Metabolism Clinics,* 45**,** 117-128.

HIROTA, T., FUJITA, Y. & IEIRI, I. 2020. An updated review of pharmacokinetic drug interactions and pharmacogenetics of statins. *Expert Opinion on Drug Metabolism & Toxicology,* 16**,** 809-822.

IGHARO, O. G., AKINFENWA, Y., ISARA, A. R., IDOMEH, F. A., NWOBI, N. L., ANETOR, J. I. & OSIBANJO, O. 2020. Lipid profile and atherogenic indices in Nigerians occupationally exposed to e-waste: a cardiovascular risk assessment study. *Maedica,* 15**,** 196.

JANSEN, I., CAHALANE, R., HENGST, R., AKYILDIZ, A., FARRELL, E., GIJSEN, F., AIKAWA, E., VAN DER HEIDEN, K. & WISSING, T. 2024. The interplay of collagen, macrophages, and microcalcification in atherosclerotic plaque cap rupture mechanics. *Basic Research in Cardiology,* 119**,** 193-213.

JIANG, S.-Y., LI, H., TANG, J.-J., WANG, J., LUO, J., LIU, B., WANG, J.-K., SHI, X.-J., CUI, H.-W. & TANG, J. 2018. Discovery of a potent HMG-CoA reductase degrader that eliminates statin-induced reductase accumulation and lowers cholesterol. *Nature Communications,* 9**,** 5138.

KHATANA, C., SAINI, N. K., CHAKRABARTI, S., SAINI, V., SHARMA, A., SAINI, R. V. & SAINI, A. K. 2020. Mechanistic insights into the oxidized low-density lipoprotein-induced atherosclerosis. *Oxidative medicine and cellular longevity,* 2020**,** 5245308.

KIM, J. J., YOON, J., LEE, Y.-J., PARK, B. & JUNG, D.-H. 2021. Predictive value of the atherogenic index of plasma (AIP) for the risk of incident ischemic heart disease among non-diabetic Koreans. *Nutrients,* 13**,** 3231.

KOPIN, L. & LOWENSTEIN, C. 2017. In the Clinic® dyslipidemia. *Annals of internal medicine,* 167**,** ITC81-ITC95.

LEE, J. & CHOI, J.-H. 2020. Deciphering macrophage phenotypes upon lipid uptake and atherosclerosis. *Immune network,* 20**,** e22.

MACH, F., BAIGENT, C., CATAPANO, A. L., KOSKINAS, K. C., CASULA, M., BADIMON, L., CHAPMAN, M. J., DE BACKER, G. G., DELGADO, V. & FERENCE, B. A. 2020. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk: The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS). *European heart journal,* 41**,** 111-188.

MC NAMARA, K., ALZUBAIDI, H. & JACKSON, J. K. 2019. Cardiovascular disease as a leading cause of death: how are pharmacists getting involved? *Integrated pharmacy research and practice***,** 1-11.

MILLS, E., WU, P., CHONG, G., GHEMENT, I., SINGH, S., AKL, E., EYAWO, O., GUYATT, G., BERWANGER, O. & BRIEL, M. 2011. Efficacy and safety of statin treatment for cardiovascular disease: a network meta-analysis of 170 255 patients from 76 randomized trials. *QJM: An International Journal of Medicine,* 104**,** 109-124.

NAIR, D., CARRIGAN, T. P., CURTIN, R. J., POPOVIC, Z. B., KUZMIAK, S., SCHOENHAGEN, P., FLAMM, S. D. & DESAI, M. Y. 2009. Association of total cholesterol/high-density lipoprotein cholesterol ratio with proximal coronary atherosclerosis detected by multislice computed tomography. *Preventive cardiology,* 12**,** 19-26.

NIROUMAND, S., KHAJEDALUEE, M., KHADEM-REZAIYAN, M., ABRISHAMI, M., JUYA, M., KHODAEE, G. & DADGARMOGHADDAM, M. Atherogenic Index of Plasma (AIP): A marker of cardiovascular.

OLAMOYEGUN, M. A., OLUYOMBO, R. & ASAOLU, S. O. 2016. Evaluation of dyslipidemia, lipid ratios, and atherogenic index as cardiovascular risk factors among semi-urban dwellers in Nigeria. *Annals of African medicine,* 15**,** 194-199.

PAPPAN, N., AWOSIKA, A. O. & REHMAN, A. 2024. Dyslipidemia. *StatPearls [Internet]*. StatPearls Publishing.

RAMKUMAR, S., RAGHUNATH, A. & RAGHUNATH, S. 2016. Statin therapy: review of safety and potential side effects. *Acta cardiologica sinica,* 32**,** 631.

RAZEGHIAN-JAHROMI, I., KARIMI AKHORMEH, A., RAZMKHAH, M. & ZIBAEENEZHAD, M. J. 2022. Immune system and atherosclerosis: Hostile or friendly relationship. *International Journal of Immunopathology and Pharmacology,* 36**,** 03946320221092188.

SADEGHI, M., HESHMAT-GHAHDARIJANI, K., TALAEI, M., SAFAEI, A., SARRAFZADEGAN, N. & ROOHAFZA, H. 2021. The predictive value of atherogenic index of plasma in the prediction of cardiovascular events; a fifteen-year cohort study. *Advances in Medical Sciences,* 66**,** 418-423.

SAMI KHAZA, M. 2013. Atherogenic index of plasma (AIP) as a parameter in predicting cardiovascular risk in males compared to the conventional dyslipidemic indices (cholesterol ratios). *Kerbala journal of medicine,* 6**,** 1506-1513.

SHAO, C., WANG, J., TIAN, J. & TANG, Y.-D. 2020. Coronary artery disease: from mechanism to clinical practice. *Coronary Artery Disease: Therapeutics and Drug Discovery***,** 1-36.

SHEEBA, D. & GANDHIMATHI, R. 2021. An Overview on Hyperlipidemia. *Journal of Pharmaceutical Research International,* 33**,** 543-555.

SUBIA JAMIL, S. J. & AFSHAN SIDDIQ, A. S. 2012. Comparison of CVD risk associated with the long term use of contraceptives in young females.

SUN, L.-Y., LEE, E.-W., ZAHRA, A. & PARK, J.-H. 2015. Risk factors of cardiovascular disease and their related socio-economical, environmental and health behavioral factors: focused on low-middle income countries-a narrative review article. *Iranian journal of public health,* 44**,** 435.

TAHA, D. A., DE MOOR, C. H., BARRETT, D. A. & GERSHKOVICH, P. 2014. Translational insight into statin-induced muscle toxicity: from cell culture to clinical studies. *Translational Research,* 164**,** 85-109.

WU, J., ZHOU, Q., WEI, Z., WEI, J. & CUI, M. 2021. Atherogenic index of plasma and coronary artery disease in the adult population: a meta-analysis. *Frontiers in Cardiovascular Medicine,* 8**,** 817441.

YıLDıZ, A., SEÇEN, Ö., YıLDıZ, C. & ÇIÇEKÇI, M. 2016. Relationship between breast arterial calcification and lipid profile, plasma atherogenic index, Castelli's risk index and atherogenic coefficient in premenopausal women. *IJC Metabolic & Endocrine,* 11**,** 19-22.

ZHOU, Q. & LIAO, J. K. 2009. Statins and cardiovascular diseases: from cholesterol lowering to pleiotropy. *Current pharmaceutical design,* 15**,** 467-478.

ZIOLKOWSKA, S., BINIENDA, A., JABŁKOWSKI, M., SZEMRAJ, J. & CZARNY, P. 2021. The interplay between insulin resistance, inflammation, oxidative stress, base excision repair and metabolic syndrome in nonalcoholic fatty liver disease. *International journal of molecular sciences,* 22**,** 11128.