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ORIGINAL RESEARCH

The Role of Interleukin-6, and IL-12+p40 in the Development of Ischemic Heart Disease

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ABSTRACT

Background: Because low-grade inflammation may play a role in the pathogenesis of coronary heart disease, and pro-inflammatory cytokines govern inflammatory cascades leading to atherosclerosis, and then to ischemic heart disease.

Objectives: To evaluate the role of two cytokines IL-6 and IL-12+p40 in the etiology of IHD, as well as to observe the relationship of IL-6 , IL-12+p40 and two chronic diseases diabetes mellitus and hypertension in IHD patients.

Methodology: A total of 70 (55 males and 15 females) patients with ischemic heart disease were included in the study. They were admitted to the Coronary Care Unit (CCU) at Ibn Al-Betar Hospital (Baghdad) for a surgical operation during the period July 2022 - April 2023. In addition to the patients, a total of 20 apparently healthy individuals (control group). Serum levels of IL-6 and IL-12+p40 were quantitatively determined in patients and control subjects by means of indirect sandwich Enzyme Linked Immuno Sorbant Assay (ELISA) test.

Results: Serum levels of IL-6 for total patients are (404.8 pg/ml), diabetic (480.3 pg/ml), non-diabetic (250.8 pg/ml), hypertensive (451.6 pg/ml) and non-hypertensive (322.2 pg/ml), patients showed a significant increased serum level of IL-6 as compared to controls (155.7 pg/ml). The diabetic patients also showed a significantly higher level than non-diabetic patients (480.3 vs. 250.8 pg/ml), as well as, hypertensive patients (451.6 pg/ml) versus non-hypertensive patients (322.2 pg/ml). Serum level of IL-12+p40 for total patients (410.2 pg/ml), diabetic (357.7 pg/ml), non-diabetic (458.1 pg/ml), hypertensive (270 pg/ml) and non-hypertensive (420.5 pg/ml) patients showed a significant decreased level of IL-12+p40 as compared to controls (649.3 pg/ml). In contrast, the non-diabetic patients showed a significantly higher level than diabetic patients (458.1 vs. 357.7 pg/ml), as well as, non-hypertensive patients (420.5 pg/ml) versus hypertensive patients (270.0 pg/ml).

Conclusion: proinflammatory cytokine cascades play crucial roles in the onset and progression of IHD.

Keywords: IL-6, IL-12+p40, IHD.

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الخلاصة

المقدمة: لأن الالتهاب منخفض الدرجة قد يلعب دورًا في التسبب في مرض القلب التاجي ، وتحكم السيتوكينات المؤيدة للالتهابات الشلالات الالتهابية والتي تؤدي الى تصلب الشرايين, وبالتالي الى مرض قصور الدورة الدموية التاجية.

الاهداف: تقييم دور الحركيان الخلويان IL12+p40 IL-6 كمسبب لمرض قصور الدورة الدموية التاجية وكذلك لمراقبة العلاقة للحركيان الخلويان IL-12+p40 , IL-6 والامراض ذات الصلة مرض السكري مرض ارتفاع ضغط الدم في مرضى قصور الدورة الدموية التاجية.

المنهجية: تضمنت الدراسة مجموع مرضى قصور الدورة الدموية التاجية 70 (55 ذكور و 15 أناث) تم دخولهم الى وحدة العناية التاجية في مستشفى أبن البيطار (بغداد) لأجراء عملية جراحية خلال الفترة من تموز 2022 الى نيسان 2023. بالإضافة الى ذلك هناك 20 فرد يتمتعون بصحة جيدة (المجموعة الضابطة). تم تحديد مستويات المصل للخلويان الحركيان IL-12+p40 , IL-6كميا في المرضى والمجموعة الضابطة عن طريق اختبار المقايسة الامتصاصية المناعية للأنزيم المرتبط indirect sandwich ELISA.

النتائج: مستويات المصل من IL-6 لإجمالي المرضى هي (404.8 بيكوغرام / مل)، ومرضى السكري (480.3 بيكوغرام / مل)، وغير مرضى السكري (250.8 بيكوغرام / مل)، وارتفاع ضغط الدم (451.6 بيكوغرام / مل) وغير المصابين بارتفاع ضغط الدم (322.2 بيكوغرام / مل)، أظهر المرضى زيادة معنوية في مستوى المصل من IL-6 مقارنة بالضوابط (155.7 بيكوغرام / مل). أظهر مرضى السكري أيضًا مستوى أعلى بكثير من المرضى غير المصابين بالسكري (480.3 مقابل 250.8 بيكوغرام / مل)، وكذلك مرضى ارتفاع ضغط الدم (451.6 بيكوغرام / مل) مقابل مرضى غير المصابين بارتفاع ضغط الدم (322.2 بيكوغرام / مل). مستوى المصل من IL-12 + p40 لإجمالي المرضى (410.2 بيكوغرام / مل)، ومرضى السكري (357.7 بيكوغرام / مل)، وغير مرضى السكري (458.1 بيكوغرام / مل)، وارتفاع ضغط الدم (270 بيكوغرام / مل) وغير المصابين بارتفاع ضغط الدم (420.5 بيكوغرام / مل) / مل) أظهر المرضى انخفاضًا ملحوظًا في مستوى IL-12 + p40 مقارنةً بالضوابط (649.3 بيكوغرام / مل). في المقابل، أظهر المرضى غير المصابين بالسكري مستوى أعلى بكثير من مرضى السكري (458.1 مقابل 357.7 بيكوغرام / مل)، وكذلك المرضى غير المصابين بارتفاع ضغط الدم (420.5 بيكوغرام / مل) مقابل مرضى ارتفاع ضغط الدم (270.0 بيكوغرام / مل).

الاستنتاج: إن انتشار IHD حسب العمر يزداد في المرضى المسنين، الذكور يظهرون نسبة إصابة أعلى من الإناث. ساهمت الأمراض المزمنة مثل ارتفاع ضغط الدم والسكري في التسبب في مرض IHD، وتلعب انسيابية الحركيات الخلوية المنشطة للالتهابات أدوارًا حاسمة في بداية وتطور مرض IHD.

الكلمات المفتاحية: IL-12+p40 ,IL-6, مرض قصور الدورة الدموية التاجية.

INTRODUCTION

Ischemic heart disease (IHD) is a narrowing of the small blood vessels that supply blood and oxygen to the heart [1]. An imbalance between coronary blood flow (supply) and myocardium oxygen consumption (demand) can precipitate ischemia, which frequently manifests as angina pectoris, when the imbalance becomes extreme, myocardial infarction (MI) may result. Congestive heart failure and arrhythmia are the major complications of MI, and arrhythmia is probably the major cause of sudden death in IHD [2], this disease is usually caused by a condition called atherosclerosis, which occurs when fatty materials and a substance called plaque are built up on the walls of arteries, leading to be narrow, as the coronary arteries narrow, blood flow can slow down or stop, causing a chest pain (stable angina), shortness of breath, heart attack, and other symptoms [3]. Recently vasoconstriction of the larger coronary vessels (spasm), whether or not it occurs in an area of an atherosclerotic plaque, has been implicated as a cause of myocardial ischemia and vasospasm may also lead to the development of a coronary thrombosis. Aortic valve diseases, hypertrophic cardiomyopathy, stenosis of the coronary ostia secondary to primary disease of the aorta, coronary embolism, inflammatory disease of the coronary arteries, and congenital syndromes such as anomalous origins of coronary arteries from pulmonary artery, are further causes of IHD [4]. The aetiology of IHD is multifactorial, in which genetic predisposition, age, gender, hypertension, diabetes mellitus, family history, infections, haemostatic factors, hyperlipidemia, physical activity, obesity, cigarette smoking, alcohol drinking, dietary factors and mental stress are important risk factors [5,6]. In addition, the severity of atherosclerosis is higher in patients with Non-typhoidal Salmonella vascular infection because it was associated with a high calcium score of the aorta, which indicative of severe atherosclerosis [7,8]. These factors are also involved in

the malfunction of the immune system, and in this regard, it has been suggested that inflammatory and immune competent cells are regular constituents of the atheromatous plaque, and they are able to produce important immunological molecules (cytokines with a special reference to interleukins), which are involved in regulating different aspects of the immune response, and according to their role in the pathogenesis of atherosclerosis, they have been classified as noxious and protective interleukins [9]. Interferon (IFN)-γ is also a further important cytokine, because T-helper-1 lymphocytes, which are believed to be largely pro-atherogenic, accumulate in the regions of plaque formation and the expression of IFN-γ is induced. Furthermore, a key role for NKT-cells, which exhibit the properties of both NK-cells and T-cells and secrete high levels of IFN-γ, has been identified in atherosclerosis, and mice with low numbers of NKT-cells displayed less atherosclerosis development than the wild type counterparts [10].

The subject of immunity in IHD can be further understood if it is considered in terms of some stress hormones, which are controlled by the sympathetic nervous system. Both systems (immune and sympathetic nervous systems) are closely linked, and this is apparent in the expression of adrenergic receptors on leucocytes and the dense innervations of lymphoid tissues [11]. Furthermore, accumulating evidences have suggested that catecholamines (CAs), the major stress hormones (adrenaline and noradrenaline), have a dual effect on cytokines, because they inhibit the production of some cytokines, while they upregulate others, therefore, they may facilitate inflammation by a dysregulation of pro-/anti-inflammatory and TH1/TH2 cytokine balance [12].

Interleukin-6 is a multifunctional pro-inflammatory cytokine produced by monocytes, macrophages, dendritic cells, mast cells, B lymphocytes, T-cells, and non-lymphocyte like fibroblast and endothelial cells, [13,14] which regulates humoral and cellular responses and plays a central role in inflammation and tissue injury. Its effects are mediated through interaction with its receptor complex; IL-6R [15,16], it can activate leukocyte and promote the release of TNF-α, that is acts as an indicator for inflammation severity [17,18,19]. This cytokine plays a very important role in the pathogenesis of coronary artery diseases (CAD), and high quantities of IL-6 have been found in human atherosclerotic plaques, and accordingly, IL-6 levels appear to be a predictive marker of future CAD [20].

Cardiovascular events are more common in patients with high circulating levels of several inflammatory markers, and treating based on inflammatory parameters, such as hs-C reactive protein (hs-CRP), have been proved to reduce outcomes [21]. Interleukin-6, however, is a central mediator of the acute-phase response and a primary determinant of hepatic production of C-reactive protein (CRP). IL-6 is associated with coronary heart disease and are not affected by other risk factors [22,23]. As hs-CRP has been classically linked to coronary events [24,25]. Data indicate a link between IL-6 and metabolism—in particular, lipid metabolism, furthermore, IL-6 is able to increase hepatic de novo synthesis of fatty acids and triglycerides, which may have harmful effects in atherosclerosis and coronary heart diseases (CHD) [26]. It also stimulates the central nervous system, leading to activation of the hypothalamus-pituitary-adrenal axis and the sympathetic nervous system, which may result in hypertension. When diabetes is considered, it has been shown that postmenopausal women with type 1 diabetes present higher serum bioactive IL-6 levels than matched healthy controls, in addition to the role of its polymorphism in increasing the genetic susceptibility for the progression of diabetic nephropathy [27].

Interleukin-6 (IL-6) is an acute-phase protein that plays a significant role in the inflammatory response, vascular inflammation, and atherosclerosis process [28,29]. It contributes to the remodeling of connective tissue by increasing metalloproteinase

gene expression. Focal overexpression of activated metalloproteinase may promote destabilization and degradation of the plaque's fibrous cap, leading to plaque instability during the atherosclerotic process [30].

Interleukin-12 is a natural killer cell stimulatory factor with a molecular weight of 75 KD, and various immune cells produce such intereukin (e.g. monocytes, macrophages, B-lymphocytes, dendritic cells and neutrophils) [31,32]. The interleukin shows an unusual heterodimeric structure that is composed of one 40 KD (P40) and one 35 KD (P35) subunits linked together by disulfide bonds.

The first subunit is secreted in a large excess over the biologically active heterodimer, and it is involved in receptor binding but P35 is necessary for a signal transduction [33]. Interleukin 12 is associated with cell-mediated immune response, and in such pathway it activates natural killer cells and cytotoxic T-lymphocytes and induces the production of interferon (IFN)-γ [34]. The potent inhibitor of IL-12 production from human peripheral blood mononuclear cells activated with Staphylococcus aureus or lipopolysaccharide (LPS) is IL-10, and the production of the free IL-12 P40 subunit is blocked by IL-10 [35]. It has been demonstrated that IL-12 presents protective effects against viral myocarditis in animal models [36]. Post-viral myocarditis develops following exposure to Cytomegalovirus (CMV), and can lead to chronic disease with end stage dilated cardiomyopathy and congestive heart failure [37,38]. This activity is enhanced by beta blockers, notably carvedilol, thus conferring a therapeutic benefit by up-regulating the production of IL-12 and IFN-γ, and by decreasing the virus load [39]. Moreover, IL-12 can significantly delay the rejection of allograft in a neonatal rat heart graft model, and this effect is mediated by nitric oxide production [40].

AIMS OF THE STUDY

1. 1-To evaluate the role of two cytokines IL-6 and IL-12+p40 in the aetiology of IHD.
2. 2-To find out the relationship between two cytokines (IL-6 and IL-12+p40), and two related diseases diabetes mellitus and hypertension in IHD patients.

METHODOLOGY

Subjects: A total of 70 (55 males and 15 females) patients with ischemic heart disease (IHD; stable angina) were included in the study. They were admitted to the Coronary Care Unit (CCU) at Ibn-Al-Betar Hospital (Baghdad) for a surgical operation during the period July 2022 - April 2023. The diagnosis was made by the consultant medical staff at the hospital. It was based on a clinical examination and other confirmatory investigations, which included electrocardiography (ECG), exercise stress test, echocardiogram, coronary CT angiography, magnetic resonance angiography (MRI) and electron-beam computed tomography (EBCT), accordingly two diseases (hypertension and diabetes mellitus) were observed in some of the IHD patients. In addition to the patients, a total of 20 healthy individuals as control groups, with no history of cardiovascular diseases, were included in the study for the purpose of comparison with patients, they were age- and gender matched with patients.

Blood Collection: five ml of peripheral blood were obtained by venipuncture from each patient before surgical operation using 5 ml disposable syringe, the blood was drawn in a plain tube (without anti-coagulant). The tubes were centrifuged (2000 rpm for 15 minutes) after 15 minutes to collect the sera, and frozen at -20ºC until tested.

Laboratory Methods: Serum levels of IL-6 and IL-12+p40 were quantitatively determined in patients and control subjects by means of indirect sandwich ELISA test using commercially available kit.

Kits: IL-6 ELISA kit: Bio-Source, Europe S.A. Cat No.MBS261259 , and IL-12+p40 ELISA kit: Bio-Source, Europe S.A. Cat No. MBS160392.

Assay Procedure:

i. Serial concentrations (they were dependent on the parameter investigated as suggested by the kit's manufacturer) of the standard were made using the diluent.

ii. An aliquot (50 µl) of the standard or sample was added to the well, and the plate was incubated for two hours at room temperature with shaking.

iii. The well was washed with three cycles of washing using the washing solution, with the aid of a micortiter plate washer.

iv. An aliquot (50 µl) of biotinylated antibody was added to the well and the plate was incubated for 30 minutes at room temperature.

v. The washing step was repeated (step iii).

vi. An aliquot (100 µl) of streptavidin alkaline phosphatase or streptavidin-HRP (it was dependent on the parameter investigated as suggested by the kit's manufacturer) conjugate was added to the well and the plate was incubated for 30 minutes at room temperature.

vii. The washing step was repeated (step iii).

viii. An aliquot (100 µl) of substrate was added to the well and the plate was incubated for 20 minutes at room temperature with shaking.

ix. An aliquot (50 µl) of stop solution was added to the well and the absorbance was read at a wave length of 450 nm using ELISA reader.

Calculations: The sample results were calculated by interpolation from a standard curve that was performed in the same assay as that for the sample (Figure 1,2), using a curve fit equation.

RESULTS:

Thirty patients from total IHD patients were observed to have diabetic mellitus, and the frequency in males was more than in females (73.3 vs. 26.7%), twenty two IHD patients were observed to have hypertension in percentage higher in males than in females (77.3 vs. 22.7%) (tables 1).

Table (1): Gender distribution of ischemic heart disease patients and controls

Subject Groups		Total Number	Males		Females	
			No.	%	No.	%
Controls		20	13	65.0	7	35.0
Patients	Total	70	55	78.6*	15	21.4
	Diabetic	30	22	73.3	8	26.7
	Non-diabetic	40	33	82.5	7	17.5
	Hypertensive	22	17	77.3	5	22.7
	Non-hypertensive	48	38	79.2	10	20.8

*** Significant difference (P ≤ 0.05) as compared the corresponding controls.**

The results obtained from this study about age group distributions of IHD patients with diabetic are higher in 60 and more age group in percentage (63.3%) , as well as in hypertensive patients in percentage (68.2%) (table 2).

Table (2): Age distribution of ischemic heart disease patients and controls

Subject Groups		Total Number	Age Groups (Years)					
			< 40		40 – 59		60 and >	
			No	%	No	%	No	%
Controls		**20**	3	15.0	14	70.0	3	**15.0**
Patients	Total	70	8	11.4	39*	55.7*	23	32.8
	Diabetic	30	2	6.7	9	30.0	19	63.3
	Non-diabetic	40	6	15.0	30	75.0	4	10.0
	Hypertensive	22	1	4.5	6	27.3	15	68.2
	Non-	48	7	14.6	33	68.8	8	16.6

* Significant difference (P ≤ 0.05) as compared the corresponding controls.

Serum levels of IL-6 for total patients are (404.8 pg/ml), diabetic (480.3 pg/ml), non-diabetic (250.8 pg/ml), hypertensive (451.6 pg/ml) and non-hypertensive (322.2 pg/ml), patients showed a significant increased serum level of IL-6 as compared to controls (155.7 pg/ml). The diabetic patients also showed a significantly higher level than non-diabetic patients (480.3 vs. 250.8 pg/ml), as well as, hypertensive patients (451.6 pg/ml) versus non-hypertensive patients (322.2 pg/ml) (table 3).

Table (3): Serum level of IL-6 in ischemic heart disease patients divided by the manifestation of diabetes mellitus and hypertension

Groups		Number	Mean± S.E. (pg/ml)
Controls		20	155.7±2.4
Patients	Total	70	404.8±12.1*
	Diabetic	30	480.3±20.4 a *
	Non-diabetic	40	250.8±18.8 b*
	Hypertensive	22	451.6±30.9 a*
	Non-hypertensive	48	322.2±12.1 b*

* Significant difference (P ≤ 0.05) as compared to the corresponding controls.

Different letters: Significant difference (P ≤ 0.05) between means of column for each clinical subgroup (diabetes or hypertensive patients).

Serum level of IL-12+p40 for total patients (410.2 pg/ml), diabetic (357.7 pg/ml), non-diabetic (458.1 pg/ml), hypertensive (270 pg/ml) and non-hypertensive (420.5 pg/ml) patients showed a significant decreased level of IL-12+p40 as compared to controls (649.3 pg/ml). In contrast, the non-diabetic patients showed a significantly higher level than diabetic patients (458.1 vs. 357.7 pg/ml), as well as, non-hypertensive patients (420.5 pg/ml) versus hypertensive patients (270.0 pg/ml) (table 4).

Table (4): Serum level of IL-12+p40 in ischemic heart disease patients divided by the manifestation of diabetes mellitus and hypertension.

Groups		Number	Mean± S.E. (pg/ml)
Controls		20	649.3±15.3
Patients	Total	70	410.2±11.6*
	Diabetic	30	357.7±17.4 a *
	Non-diabetic	40	458.1±14.7 b*
	Hypertensive	22	270.0±19.0 a*
	Non-hypertensive	48	420.5±13.2 b*

* Significant difference (P ≤ 0.05) as compared the corresponding controls.

Different letters: Significant difference (P ≤ 0.05) between means of column for each clinical subgroup (diabetes or hypertension).

DISCUSSION

Stable angina is the most prevalent manifestation of coronary artery disease (CAD). Its prevalence increases with age, and despite a higher overall incidence and prevalence of coronary disease in men than in women [41], such observation can also be explained in the ground of estrogen level, which appears to be a heart protective playing a role in the manifestation of CVD by increasing HDL and reducing LDL, probably by increasing the number of LDL receptors on the liver cells (removing LDL from the blood). Therefore, it is generally believed that pre-menopausal women have such a lower incidence of heart disease than men [42].

Stable angina pectoris was significantly increased in older aged patients of both males and females, and such increase can be positively correlated with the increasing plasma levels of adrenaline and noradrenaline as these two hormones normally show an increased level as age is progressed in both males and females, and such findings have been demonstrated by Rachel and Ramarson [43], who reported that the incidence of cardiovascular events is more predominant in elderly peoples, increase production of IL-6 can stimulate the central nervous system, which in turn activates the sympathetic nervous system, stimulates hypothalamus pitutary adrenal axis and stimulates adrenal gland to produce more adrenaline and noradrenaline, this explanation is in agreement with such outcome of Straub et al. [44], who found that the improve activation of the hypothalamus-pitutary-adrenal axis and sympathetic nervous system as a result of increased IL-6 secretion in postmenopausal women.

A further augmentation of the subject have recently been addressed by Jankord et al. [45], who also reported that aging will progressively increase CAs. Such demonstration can be explained in the ground of inflammation, which appears to be a common underlying background that has been termed atherosclerosis, and in this sense, diabetes mellitus may accelerate atherosclerosis [46]. It was reported that the patient with type II diabetes have two- to four-fold increased risk for CHD, and more than 50% of all diabetic patients die of CHD [47]. Additionally, inflammation is emerging as an important mechanism for micro- and macro-vascular complications of diabetes [48]. In this regard, macrophage plays a key role in the chronic inflammatory response by by secreting proinflammatory cytokines and chemokines and producing reactive oxygen species, thus it is accelerated atherosclerosis and altered vascular wall function [49].

Insulin stimulates IL-6 production by adipocytes, and is often characterized by hyperinsulinemia, IL-6 in turn stimulates the central

nervous system, leading to the activation of hypothalamus-pituitry-adrenal axis and the sympathetic nervous system to secret adrenaline and noradrenaline [50]. A significantly increased level of IL-6 in the present sample of IHD patients supports such view, especially in diabetic patients, in whom adrenaline and noradrenaline levels together with IL-6 level were significantly increased.

Hypertension results from increased peripheral vascular smooth tone, which leads to increased arteriolar resistance and reduced capacitance of the venous system. These consequences can lead to coronary heart disease [51]. The pathogenic mechanisms behind hypertension are still disputed, but they most probably involve damage to the vascular endothelium, which increases the risk of clot formation and coupled with an increased myocardial oxygen demand, moreover, hypertension was increased in response to stress, because adrenaline stimulates α, β1 and β2 receptors in vascular smooth muscle cells [52].

The mean serum level of IL-6 was significantly increased in IHD patients, and such elevation can be explained through inflammatory and immune competent cells that are regular constituents of the atheromatous plaque, because phagocytic cells are able to take up lipids and may degenerate to form foam cells. Such cells produce their typical cytokines such as IL-6, which explains the presence of large quantities of this pro-inflammatory factor within the plaque and plays a very important role in the pathogenesis of CAD [53], as well as, this result can also be explained by the association of increased IL-6 with elevated fibrinogen levels, which leads to an increased tendency to thrombosis [54].

The mean serum level of IL-6 was also increased in diabetic patients, and such result can be explained by insulin, because it stimulates IL-6 production by adipocytes and can potentially provide an explanation for the elevated IL-6 concentration observed in obesity, which is often characterized by hyperinsulinemia. Additionally, it has also been shown that postmenopausal women with diabetes present higher serum IL-6 levels than matched healthy controls [55].

The mean serum level of IL-6 was significantly increased in hypertensive patients, and it was associated with increased mean plasma level of CAs in the patients. The IL-6 is able to stimulate the central nervous system leading to the activation of the sympathetic nervous system, which may result in hypertension [56]. Clinically, elevated serum levels of pro-inflammatory cytokine interleukin-6 is a prognostic indicator for future cardiac events and cardiac morbidity [57].

The mean serum level of IL-12+p40 was observed at a significantly lower level in patients with IHD, and this level was also decreased with the elevation of CAs level. Such finding is in agreement with the results of Calcagni and Elenkov [58], who demonstrate that the increasing CAs concentrations can induce an inhibition of IL-12 production. The mean serum level of IL-12+p40 was decreased in diabetic patients, an observation that may suggest that this cytokine is involved in glucose metabolism, in this regard, initial data indicate a favorable action on glucose metabolism, and T lymphocyte activation induced by IL-12 was associated with an increased expression of glucose transporter-like protein [59]. However over, IL-12 produced by macrophages in chronic inflammatory response of diabetic patients have been associated with accelerated atherosclerosis and altered vascular wall function [60].

Inflammation plays a major role at all stages of the atherosclerotic process, from the early events whereby leukocytes are recruited at sites of sub endothelial LDL cholesterol accumulation to the late events, when plaque rupture occurs, leading to thrombus formation and adverse clinical outcomes. The chronic inflammatory disease of the arterial wall is promoted by both innate and adaptive Th1-driven immunity and is orchestrated by a complex network of proinflammatory cytokines [61,62].

CONCLUSION

The prevalence of IHD according to age are increased in older aged patients, the male show high infected percentage than female. Chronic diseases like hypertension and diabetes mellitus were contributed to the pathogenesis of IHD, and proinflammatory cytokine cascades play crucial roles in the onset and progression of IHD.

RECOMMENDATIONS

Targeting cytokines in an attempt to develop pharmacological activators of some interleukins, and inhibitors of other ones, and this may provide effective means to control atherosclerosis and associated diseases (i.e. diabetes mellitus and hypertension).

Ethical Clearance: All experimental protocols were approved under the Faculty of science.

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FIGURES

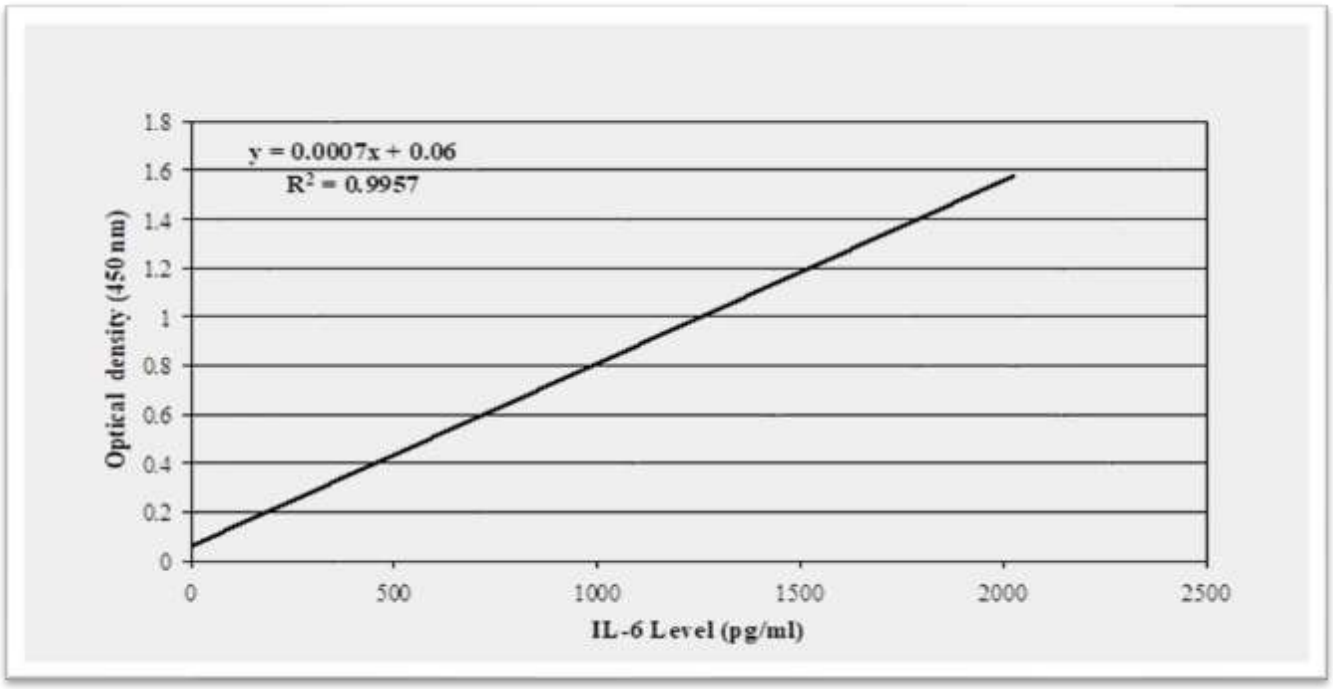

Figure (1): Standard curve of IL-6 serum level

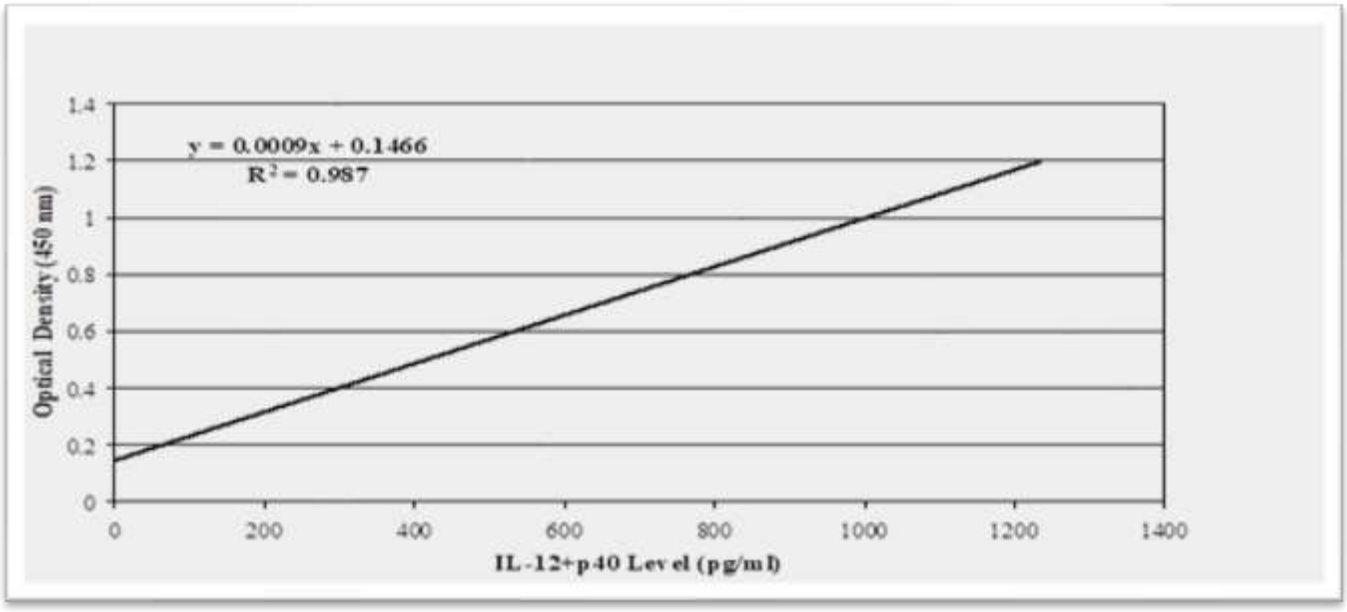

Figure (2): Standard curve of IL-12+p40 serum level.