SunKrist Publishing
Accelerate Scientific Knowledge in Open Access

SunKrist Endocrinology and Metabolism Research Journal

Mini Review Article *Volume: 2, Issue: 1* *Scientific Knowledge*

IL-6 As a Surrogate Biomarker in Inflammatory Heart Disease: Cytokines Role in the Pathogenesis of Cardiovascular Diseases

Rafik R[1*], Andrew RR[1], Mark RR[1] and Alaa I[2]

[1]Canada Metabolic Inflammation Diagnostics Inc. (CMID INC.) - Toronto, Canada

[2]Lake Mary, Pulmonary and critical care Medicine -Florida, USA

1. Abstract

Inflammatory cytokines are strongly involved in the development of inflammatory heart diseases that can be the leading cause for coronary artery disease, myocardial infarction, heart failure and other chronic diseases. Among the biomarkers that are accompanying low grade inflammation include IL-1β, IL-6, IL-10, macrophage migration inhibitory factor and TNF-α. The role of inflammatory cytokines is considered as a causative factor in the development of atherosclerotic process. The current review points out the importance of measuring the inflammatory biomarkers both IL-1β and IL-6 as a screening laboratory tests with diagnostic and therapeutic value in clinical practice.

2. Keywords: Clinical Biochemistry; Molecular; Diagnostic; Endocrinology; Cardiovascular diseases; Atherogenesis; Free Fatty Acids (FFAs) and Interleukin 1β (IL-1β) and Interlukin-6 (IL-6)

3. Introduction

This review outlines and focuses on the specificity in determining the high risk individuals and patients through the measurements of screening inflammatory biomarkers as IL-1β, IL-6 and TNF- α in diagnostic laboratories. Inflammation process is categorized into two episodes, acute and chronic responses. The acute inflammatory response is a rapid response with short duration [1]. It is caused by the migration of neutrophils and exudation of plasma proteins and fluids into the injured site. However, chronic inflammation is a response that occurs through the presence of macrophages and lymphocytes with long term duration. The inflammatory response might leads to the development of a variety of diseases including the initiation of atherosclerotic process. This impacts adversely on vascular function leading to heart diseases and resulting in congestive heart failure (CHF) [2-3].

The inflammatory mediators, cytokines are glycoproteins in structure or regulatory soluble proteins of low molecular weight secreted by different cell types including WBCs. Various cytokine molecules modulate the proliferation and differentiation of immune cells [4-9]. Cytokines are also known as lymphokines, monokines and interleukins as they are secreted by lymphocytes, monocytes and leukocytes accordingly.

Moreover, one particular type of cytokines such as monocyte inflammatory protein (MIP-1α and MIP-

*Corresponding author: Dr. Rafik Ragheb, PhD, Clinical Scientist/Director at Canada Metabolic Inflammation Diagnostics Inc. (CMID Inc.), Toronto, Canada and Program Chair, Medical laboratory Department - Anderson College, Toronto, Canada, Tel: 1-6474013185, E-mail: rafik.ragheb@utoronto.ca

Received Date: April 17, 2021; Accepted Date: April 20, 2021; Published Date: April 24, 2021

1β), monocyte chemoattractant protein (MCP-1). Lymphocytes and activated tissue macrophages primarily secrete inflammatory cytokines in response to various inflammatory stimuli, such as endotoxin, chemical and physical injury [10]. There are two major groups of inflammatory cytokines: one group is responsible for acute inflammation and other group is involved in chronic inflammation. Acute inflammation is caused by cytokines such as interleukin (IL)-1, IL-6, IL-8, IL-11, TNF-α (tumor necrosis factor-α), IL-16, IL-17, G-CSF (granulocyte colony stimulating factor) and GM-CSF (granulocyte-macrophage colony-stimulating factor) [11]. The inflammatory cytokines in chronic inflammation can be subdivided into two classes: cytokines. One class is coordinating humoral responses are IL-4, IL-5, IL-6, IL-7 and IL-13. The other class is coordinating cellular responses are IL-1, IL-2, IL-3, IL-4, IL-7, IL-9, IL-10, IL-12, interferons TNFα and β. Few of these cytokines are significantly playing a role in both acute and chronic inflammation, as IL-1, IL-6, IL-11, IL-17 and TNF-α [12]. This review highlights the role of inflammatory cytokines in the pathogenesis of cardiovascular diseases (CVDs).

3.1. What is IL-6?

Interleukin 6 (IL-6) is known as a B cell differentiation factor [13]. It is an expressed protein found in different cell types including immune cells, endothelial cells, skeletal and smooth muscle cells, thyroid cells, fibroblasts, mesangial cells, keratinocytes, microglial cells, astrocytes, certain tumor cells and islet β-cells [14]. It has been reported that IL-6 is involved in inflammatory processes as hematopoiesis, liver and neuronal regeneration [15-16]. The synthesis of IL-6 and its secretion are induced upon stimulation of Toll-like receptor (TLR) by lipopolysaccharide or upon stimulation of cells by interleukin 1 (IL-1) or tumor necrosis factor (TNF). Further, IL-6 is unique as it influences various cell types and has both pro- and anti-inflammatory effects [17]. Strong body of literatures have shown that dysregulation of IL-6 signaling has been implicated in the pathogenesis of several autoimmune and inflammatory diseases including T2D [14]. The focus of the current article is to illustrate IL-6 linked insulin resistance involvement in the development of T2D. Other reports have shown different actions orchestrated by IL-6 and insulin resistance development [18]. Here, we provide an overview of IL-6 as a surrogate biomarker to assist in the diagnosis as a tool for monitoring T2D treatment efficacy.

3.2. The link between IL-6 and pathogenesis of cardiovascular diseases

Research studies in human populations have shown that pro-inflammatory cytokines, acute phase proteins and several indirect markers of inflammation to consider as predictors of T2D and glucose disorders in relation to FFA elevation [19]. Interestingly, interleukin-6 (IL-6) levels have been reported to be elevated in subjects with T2D [20] and correlates directly and indirectly with insulin resistance [21] and other cardiovascular and immunological disorders. Cytokine receptor activation activates signaling pathways that directly or indirectly impair insulin action. Efforts are made to decipher the close mechanistic relation between cytokine receptor activation and impaired insulin signaling. It has been shown a pleiotropic effector of both cytokine signaling and ER stress. For example, JNK. JNK induces a complex pro-inflammatory transcriptional program that directly phosphorylates IRS1. In addition, JNK activity is increased in obese insulin-resistant liver and skeletal muscle [21]. A strong body of literature documented the inflammatory markers IL-6 and TNFα. They are playing a major role in the pathophysiology of metabolic syndrome and T2D development [22-26]. This highlights the importance of measuring the inflammatory proteins in the clinical setting. Normal cellular fatty acid balance reflects on the equilibrium between processes that generate or deliver FFAs and processes that utilize it. FFAs are

generated through the de-novo synthetic pathway and liberated when triglycerides and phospholipids are hydrolyzed by lipases [27]. High plasma FFAs and triglyceride levels cause an increased flux of FFAs into non-adipose tissues, contributing to intracellular lipid accumulation. Non-adipose tissues such as liver and skeletal muscle [28] have a limited capacity for lipid storage leading to cellular disturbances, the phenomenon that is known as lipotoxicity. Studies have documented that primary hyperlipidemia, serum triglycerides [29-3]) and FFAs [30-31] are elevated in type 1 diabetes and T2D in obese individuals [32]. Insulin resistance is believed to be the primary cause of T2D. Studies have shown that elevated plasma levels of FFAs might increase insulin resistance in muscle and liver. So, lowering the levels of FFAs is considered a potential therapeutic target for T2D. Our previous research work was focused on elucidating the molecular mechanisms by which FFAs induce insulin resistance in two insulin sensitive tissues, muscle and liver. Specifically, we investigated in details the mechanisms and the effects of two FFAs the oleate, the monounsaturated FFA (18:1) and palmitate, the saturated FFA (16:00) as they are the most predominant two fatty acids in the circulation [32]. We studied their effect on glucose metabolism and insulin action in two insulin sensitive tissues the muscle and the liver and investigated on how they can induce the insulin resistance at the molecular level in vitro in two different experimental designs for insulin resistance [33-35]. There is a strong correlation between insulin resistance and the increased lipid availability in the muscle tissue as manifested from the literature and our own data. Several mechanisms that affect insulin signal transduction have been identified [36].

In our laboratory we found that oleate does not affect the total protein level of PKB/Akt total but partially reduces the phosphorylation of PKB in oleate and dramatically in palmitate treated cells. On the other hand, our data suggest that the monounsaturated fatty acid; oleate muscle insulin resistance mainly via PKC. In the contrary, the saturated fatty acid, palmitate induces insulin resistance mechanistically through the PKB inhibition that is well documented through the ceramide formation and PP2A activation. In addition, the two FFAs are also to activate the NFκB and the stress kinases that contribute to the induction of serine 307 phosphorylation of IRS-1 and the development of insulin resistance in the C2C12 muscle model [33-35]. The serine 307 phosphorylation of IRS-1 is considered as a potential therapeutic target for the early intervention with the onset of the disease. Wang C et. al. have reported that palmitate specifically induced insulin resistance by PKC theta-dependent activation of mTOR/S6K pathway in C2C12 myotubes [37] However, more studies are still required to further elucidate the exact consequences of PKC activation following FFA(s) treatment with other species.

Furthermore, our second set of data is to represent the experimental work that was conducted in the fructose fed hamster as a liver model for diet induced insulin resistance. The data pointed the FFA – induced PKC activation and its impact on dyslipidemia seen in the liver model. The fructose fed hamster model as a model of diet induced model for studying insulin resistance in the liver, has revealed the importance of PKC activation for both insulin resistance and de novo lipogenesis. As reported Ragheb R. et al. have demonstrated that the antioxidant, Taurine was capable of reversing oleate-induced insulin resistance in myocytes as manifested from the glucose uptake data [31]. Han P. et.al have also reported that Taurine prevented FFAs-induced hepatic insulin resistance in association with inhibiting JNK1 activation and improving insulin signalling in vivo [39]. Taurine is considered as a potential therapeutic target in protecting from insulin resistance caused by elevated FFAs caused by different mechanisms of oxidative stress and inflammatory pathways. Further, we highlights the clinical importance for measuring the

inflammatory biomarkers for diagnostic and monitoring the therapy efficacy [40]. Specifically, the inflammatory markersIL-1β, IL-6 and TNFα are among the key players that are manifesting a major role in the pathophysiology of insulin resistance syndrome and type 2 diabetes development and it can be the leading cause in other diseases including cardiovascular diseases (CVD) [41] The excess of lipids (Lipotoxicity) in the cardiomyocytes result in disruption of several signaling pathways and CVD development.

3.3. The pathogenesis of Inflammatory Heart disease (IHD)

IHD are a group of disorders that affect different layers of the heart. These include pericarditis, myocarditis and endocarditis. IHD can originate from auto inflammatory diseases that results in the disease phenotype development [42-43]. Acute pericarditis is inflammatory recurrent acute pericarditis (IRAP), which occurs in 15% - 30% of patients due to auto inflammatory or autoimmune events [44]. Impaired function of the innate immune system resulting in auto inflammatory Pericarditis can occur due to mutations in immune response [45]. Pericardial fluid not plasma samples, may contain inflammatory mediators like IL-6, IL-8 IFN-γ with a preferential detection of anti-myolemma over anti-sarcolemma antibodies, implying that local autoimmune events can occur specific to the heart [46]. Whereas the appearance of cardiac troponin-T (cTnT) signifies occurrence of acute and recurrent pericarditis [47]. Myocarditis is a disease that impacts cardiac myocytes, interstitial or and vascular element. It is manifested through perimyocarditis development at the level of pericardium with the involvement of lymphocytes and macrophages as a leading cause of heart failure and sudden death or dilated cardiomyopathy [48-49]. Myocarditis is common in young men than women [50]. Endocarditis is a disease that occurs due to infection or non-infection sources. The endocardium damage can result from valve sclerosis, rheumatic valvulitis or through bacterial vegetation [51]. Endocarditis can impact the heart leading to valve and endothelial scarring and resulting in congestive heart failure [51]. This might occur in autoimmune diseases as rheumatic arthritis (RA) and systemic lupus erythematosus (SLE) [52].

3.4. The importance of using the cytokine biomarkers for screening, prevention and early diagnosis

Many reports have revealed that macrophages are central mediators of inflammation in both cardiovascular diseases and T2D. These cells are classified into two distinct sub-types: the classically activated macrophages known as M1. The M1 cells are to secrete pro-inflammatory cytokines including IL-6. However, the activated macrophages termed M2 are to secrete anti-inflammatory cytokines [53]. The M1 macrophage infiltration into insulin sensitive tissues and pancreatic islets increases the development of a low grade inflammation [54]. Together adipose cells and mast cells exacerbate insulin resistance and promote glucose intolerance by producing IL-6 and interferon-γ [55]. In addition, it has been reported that neutrophils play an important part in the regulation of IL-6 signal-ling during inflammatory process. Neutrophils are among the first cells to accumulate at the sites of inflammation [32]. The above data, clearly highlights the importance of having the measurements of the inflammatory markers as a diagnostic tool to screen and predict those patients that their basal level is showing a higher levels of the inflammatory cytokines in the circulation.

3.5. Clinical significance of IL-6

Many published studies and reports have suggested that IL-6 contributes to the onset and progression of chronic inflammation diseases such as T2D and cardiovascular disorders [56]. The pathological role of IL-6 is further supported by research work whereby IL-6 blockade (using anti-IL-6 or anti-IL-6R antibodies, or IL-6 −/− mice) demonstrated

preventive and suppressive effects on the development of various immune-related disorders. Important to note, the humanized anti-IL-6R antibody tocilizumab has been approved for the treatment of Rheumatoid Arthritis (RA) in more than 100 countries. Tocilizumab mode of action is through the inhibition of binding IL-6 to both mbIL-6R and sIL-6R that results in complete blockade of IL-6 signaling [57,58]. Tocilizumab and other anti-IL-6R antibodies have shown promising results in the treatment of other immune-related disorders [59]. Tocilizumab has been reported to improve insulin sensitivity and decrease glycated hemoglobin (HbA1c) levels in humans [60,61]. The current data support the notion that IL-6 signaling is a potential therapeutic target for the treatment of inflammatory-mediated disorders.

Tocilizumab and many other IL-6R anti-bodies block both classic and trans-signaling of IL-6. This global inhibition of IL-6 signaling pathways, disrupts both pro- and anti-inflammatory activities of the cytokine and may result in various physiological dysfunctions. Moreover, global IL-6 blockade has been associated with increased risk of bacterial infections, liver malfunction elevation of cholesterol and weight gain [57,58]. These findings have led to the suggestion that specific inhibition of trans-signaling, as compared to the global inhibition of IL-6, may result in better therapeutic outcomes with fewer undesired side effects. The sgp130Fc protein is a recombinant version of sgp130, which consists of the extracellular portion of gp130 fused to the Fc region of a human immunoglobulin G1 (IgG1) anti-body. Sgp130Fc specifically blocks IL-6 trans-signaling, without affecting classical IL-6 signaling. Therefore, sgp130 inhibits the pro-inflammatory actions of IL-6, while leaving its anti-inflammatory and protective activities intact. Sgp130Fc has demonstrated robust efficacy in the treatment of many autoimmune and inflammatory diseases, with better side effect profile than global blockers of IL-6 signaling [59-61]. Sgp130Fc selectively blocks the chemotactic signaling mediated by sIL-6R, therefore prevents high fed diets induced-macrophage infiltration into obese adipose tissue [62]. In addition, treatment with sgp130Fc significantly reduces atherosclerosis, decreases expression of endothelial adhesion molecules and intimal smooth muscle cell infiltration thus reduces monocyte recruitment and the subsequent progression of atherosclerotic plaques [63]. Moreover, none of the adverse effects of complete IL-6 blockade was demonstrated with sgp130Fc [62-63].The above-mentioned data clearly highlight the therapeutic potential of selective inhibition of IL-6 trans-signaling for treatment of T2D and its vascular complications. Furthermore, given the specificity of sgp130Fc to inhibit trans-signaling, this protein can be used as a molecular tool to identify whether a certain effect of IL-6 (e.g. effect of IL-6 on glucose metabolism) is mediated via classic or trans-signaling [59]. This approach could be particularly useful to study the signaling pathways of IL-6 in mb-IL-6R expressing cells (e.g. hepatocytes and pancreatic islet cells), which can be stimulated by both the classic and trans-signaling pathways. Therefore, in addition to its therapeutic properties, the sgp130Fc protein allows us to discriminate between different IL-6 signaling pathways and thus advance our knowledge on the pathophysiological role of IL-6 signaling in the development of T2D in different tissues and contexts. This pleiotropic nature is at least in part dependent on the signaling pathway which is activated by IL-6. Increasing evidence from clinical and animal studies suggest that, in many inflammatory conditions, selective blockade of trans-signaling is therapeutically more effective and safer than global inhibition of IL-6, supporting the concept that pro-inflammatory and harmful activities of the cytokine are mainly mediated via trans-signaling. Of particular note, the sgp130Fc protein, which is a specific inhibitor of IL-6 trans-signaling, has been shown to completely prevent macrophage infiltration into obese adipose tissue and significantly reduce the extent of

atherosclerosis. These results indicate that specific blockade of IL-6 trans-signaling with sgp130Fc could be considered as a potential therapeutic strategy for treatment of T2D and its macrovascular complications. Blockade of IL-6 trans-signaling, in combination with other anti-inflammatory treatments, such as anti-IL-1β agents have been reported. Anakinra, is a biologic drug acts as an antagonist for IL-1 activity that is used for the treatment of Rheumatoid Arthritis (RA) and other auto-immune disorders. Anakinra, effectively decreased glycated (HbA1C) in the circulation with the increase of C-peptide level after 13 weeks of treatment [64]. Furthermore, anakinra showed an improvement of the glucose disposition index during oral glucose tolerance test in obese patients without T2D [65]. Similar results were shown in patients with impaired glucose tolerance represented a significant improvements of insulin secretion after 4 weeks of anakinra treatment [66]. Other reports showed Gevokizumab that reduced HbA1C level as well in T2D patients with 0.03-0.1 mg/kg dosage [67-68]. In addition, Canakinumab is a biologic treatment that inhibits IL-1β that improved the fasting glucose and insulin section after 4 weeks of treatment [69]. These evidences manifest the importance of the inflammatory cytokine measurements as a diagnostic tool to closely monitor and guide for the development of more efficacious strategies for early intervention and treatment of cardiovascular disorders, T2D and autoimmune disorders.

4. Conclusion

This review has outlined the importance of IL-6 as a surrogate markers and its clinical value for screening and early prediction of inflammatory heart disease, T2D and autoimmune disorders in the diagnostic laboratories.

Our research work data showed a direct evidence for the desensitization of muscle cells following FFAs exposure. Furthermore, the data have demonstrated the importance of PKC activation in two different models for FFAs induced insulin resistance, the muscle and liver that impact the inflammation process. In 1997, the WHO has recognized the importance of insulin resistance and its link to T2D, the growing problem that of great deal for the public health globally. Further insight to the field will be invaluable and of great impact on the treatment and the early intervention of the disease onset that is tightly linked to a number of other diseases such as lipid disorders, cardiovascular and autoimmune diseases that are accompanied with low grade inflammation. In addition, the early measurement of the inflammatory biomarkers, IL-6, IL-1β, TNFα and FFAs levels in plasma have a great clinical significance. As discussed IL-6 utilization as a diagnostic tool would benefit patients with insulin resistance syndrome through the implementation of an early intervention protocols for preventing and early diagnosing of pre-diabetic patients. Furthermore, the measurement of cytokines is considered as a potential diagnostic tool to control the growing epidemic of diabetes and cardiovascular complications by monitoring closely the efficacy of different treatment regimens being followed.

5. Declaration

The authors have no affiliation of financial involvements, interest or conflict with any organizations.

6. Acknowledgement

Dr. Rafik Ragheb is grateful for the collaborative efforts with Dr. Alaa Iskandar.

We are so appreciative to have our research assistants and volunteers for their help and input with research activities (screening selection of articles used for our mini-review).

We thank all authors of the original published articles. Finally, we thank all participants for identifying new means to improve diagnostic methodology protocols conducted in our laboratory by having a new insight to impact on cardiovascular, diabetes and autoimmune disease treatment and diagnosis.

References

1. Iwalewa EO, McGaw LJ, Naidoo V, Eloff JN. Inflammation: the foundation of diseases and disorders: a review of phytomedicines of South African origin used to treat pain and inflammatory conditions. African J Biotechnol 2007; 6: 2868-2885.
2. Wang Z, Nakayama T. Inflammation, a link between obesity and cardiovascular disease. Mediators Inflamm 2010; 2010: 535918.
3. Petrukhin IS, Lunina EY. Cardiovascular disease risk factors and mortality in Russia: challenges and barriers. Public Health Rev 2011; 33: 436.
4. Ashley NT, Weil ZM, Nelson RJ. Inflammation: mechanisms, costs and natural variation. Annu Rev Ecol Evol Syst. 2012; 43: 385-406.
5. Coussens LM, Werb Z. Inflammation and cancer. Nature. 2002; 420: 860.
6. O'Byrne KJ, Dalgleish AG. Chronic immune activation and inflammation as the cause of malignancy. Br J Cancer. 2001; 85: 473.
7. Lho Y-M, Ha E, Cho C-H, Song KS, Min BW, Bae KC, et al. Inflammatory cytokines are overexpressed in the subacromial bursa of frozen shoulder. JShoulder Elbow Surg. 2013; 22: 666-672.
8. Bunker TD, Reilly J, Baird KS, Hamblen DL. Expression of growth factors, cytokines and matrix metalloproteinases in frozen shoulder. J Bone Joint Surg Br. 2000; 82: 768-773.
9. Dinarello CA. Proinflammatory cytokines. Chest. 2000; 118: 503-508.
10. Pober JS, Cotran RS. The role of endothelial cells in inflammation. Transplantation. 1990; 50: 537-544.
11. Feghali CA, Wright TM. Cytokines in acute and chronic inflammation. Front Biosci 1997; 2: d12-d26.
12. Baker KJ, Houston A, Brint E. IL-1 family members in cancer; two sides to every story. Front Immunol. 2019; 10: 1197.
13. Hirano T, Taga T, Nakona N, Yasukawa K, Kashiwamura S, Shimizu K, et al. Purifcation to homogeneity and characterization of human B-cell diferentiation factor (BCDF or BSFp-2). Proc Natl Acad Sci USA. 1985; 82: 5490-5494.
14. Kamimura D, Ishihara K, Hirano T. IL-6 signal transduction and its physiological roles: the signal orchestration model. Rev Physiol Biochem Pharmacol. 2003; 149: 1-38.
15. Rothaug M, Becker-Pauly C, Rose-John S. The role of interleukin-6 signaling in nervous tissue. Biochim Biophys Acta. 2016; 1863: 1218-1227.
16. Scheller J, Grotzinger J, Rose-John S. Updating interleukin-6 classic-and trans-signaling. Signal Transduct. 2003; 6: 240-259.
17. Hunter CA, Jones SA. IL-6 as a keystone cytokine in health and disease. Nat Immunol. 2015; 16: 448-457.
18. Pedersen BK, Febbraio MA. Interleukin-6 does/does not have a benefcial role in insulin sensitivity and glucose homeostasis. J Appl Physiol. 2007; 102: 814-816.
19. Wilding JP. The importance of free fatty acids in the development of Type 2 diabetes Diabetic Medicine (24). 2007; 9: 934-945.
20. JM Fernandez-Real, M Vayreda, C Richart, C Gutierrez, M Broch, J Vendrell, et al . Circulating Interleukin 6 Levels, Blood Pressure and Insulin Sensitivity in Apparently Healthy Men and Women. J Clin Endocrinology & Met. 2001; 86: 1154-1159.
21. Hirosumi J, Tuncman G, Chang L, Görgün CZ, Uysal KT, Maeda K, et al. A central role for JNK in obesity and insulin resistance. Nature. 2002; 420: 333-336.
22. Abhishek Chauhan, Suraj S, Pradeep D, Nand L, Kauser U, Sanjay K. Correlation of Serum and Salivary Cytokines Level with Clinical Parameters in Metabolic Syndrome With Periodontitis. J Clin Laboratory Analysis. 2016; 30: 649-655.

23. Hoang Van Tong, Nguyen KL, Ho SS, Nguyen VH, Trinh TH, Thirumalaisamy PV, et al. Adiponectin and pro-inflammatory cytokines are modulated in Vietnamese patients with type 2 diabetes mellitus. J Diabetes Investigv. 2017; 8: 295-305.

24. Undurti N Das. Is there a role for Bioactive Lipids in the pathobiology of diabetes Mellitus? Front Endocrinol (Lausanne). 2017; 8: 182.

25. Federica Z, Michele L, Jamal N, Gregory AR, Antonella D, Claudia M, et al. Chronic Adipose Tissue Inflammation Linking Obesity to Insulin Resistance and Type 2 Diabetes. Front Physiol. 2020; 10: 1607.

26. Thabsile M, Phiwayinkosi VDC, Tawanda MN, Vuyolwethu M, Sithandiwe E M-M, et al. A systematic review on the functional role of Th1/Th2 cytokines in type 2 diabetes and related metabolic complications. Cytokine. 2020; 126.

27. Schaffer JE. Fatty acid transport: the roads taken. Am J Physiol Endocrinol Metab. 2002; 282: E239-E246.

28. Garg A. Lipodystrophies. Am J Med. 2000; 108: 143-152.

29. Hallgren B, Stenhagen S, Svanborg A, Svennerholm L. Gas chromatographic analysis of the fatty acid composition of the plasma lipids in normal and diabetic subjects. J Clin Invest. 1960; 39: 1424-1434.

30. Laakso M, Pyorala K, Voutilainen E, et al. Serum lipids and lipoproteins in middle-aged non-insulin-dependent diabetics. Atherosclerosis. 1985; 56: 271-281.

31. Fraze E, Donner CC, Swislocki ALM, Chiou YA, Chen YD, Reaven GM. Ambient plasma free fatty acid concentrations in noninsulin-dependent diabetes mellitus: evidence for insulin resistance. J Clin Endocrinol Metab. 1985; 61: 807-811.

32. Zuniga-Guajardo S, Zinman B. The metabolic response to the euglycemic insulin clamp in type I diabetes and normal humans. Metabolism. 1985; 34: 926-930.

33. Campbell PJ, Carlson MG, Nurjhan N. Fat metabolism in human obesity. Am J Physiol. 1994; 266: E600-E605.

34. Rafik Ragheb, Gamila M L Shanab, Amina M Medhat, Dina M Seoudi, K Adeli, G I Fantus. Free fatty Acids - induced muscle insulin resistance and glucose uptake dysfunction: Evidence for PKC activation and oxidative stress activated signaling pathways. Biochem Biophys Res Commun. 2009; 389: 211-216.

35. Rafik Ragheb, Amina M Medhat, Gamila M L Shanab, Dina M Seoudi, I G Fantus. Prolonged Treatment with free fatty acids has post receptor effect in hepatic insulin resistance: Evidence that free fatty acids, oleate and palmitate have insignificant effect on the insulin receptor beta in vivo and ex vivo primary hepatocytes. Biochem. Insights. 2009; 2: 29-36.

36. Rafik Ragheb, Amina M Medhat, Gamila M L Shanab, Dina M Seoudi, I G Fantus. Links between enhanced Fatty Acid Flux, Protein Kinase C and NFκB Activation and ApoB-Lipoprotein Production in the Fructose Fed Hamster Model of Insulin Resistance. Biochem Biophys Res Commun. 2008; 370: 134-139.

37. Leskinen MH, Solakivi T, Kunnas T, Alho H, Nikkari ST. Serum fatty acids in postinfarction middle-aged men. Scand. J Clin Lab Invest. 2005; 65: 485-490.

38. Wang X, Yu W, Nawaz A, Guan F, Sun S, Wang C. Palmitate induced insulin resistance by PKCtheta-dependent activation of mTOR/S6K pathway in C2C12 myotubes. Exp Clin Endocrinol Diabetes. 2010; 118: 657.

39. Wu N, Lu Y, He B, Zhang Y, Lin J, Zhao S, et al. Taurine prevents free fatty acid-induced hepatic insulin resistance in association with inhibiting JNK1 activation and improving insulin signaling in vivo. Diabetes Res Clin Pract. 2010; 90: 288-296.

40. Rafik R Andrew RR, Mark RR. Lipid-Induced Insulin Resistance Mechanisms: The Link to Inflammation and Type 2 Diabetes. SunKrist Endocrinol and Metab Res J. 2021; 2: 1-9.

41. Rader DJ. Effect of insulin resistance, dyslipidemia and intra-abdominal adiposity on the development of cardiovascular disease and diabetes mellitus. Am J Med. 2007; 120: S12-S18.

42. Fairweather D, Rose NR. Inflammatory heart disease: a role for cytokines. Lupus. 2005; 14: 646-651.

43. Lu L, Sun R, Liu M, Zheng Y, Zhang P. The inflammatory heart Diseases, causes, symptoms and treatments. Cell Biochem. Biophys. 2015; 72: 851-855.

44. Lazaros, G., Antonatou, K. and Vassilopoulos, D.The therapeutic role ofInterleukin-1 inhibition in idiopathic recurrent pericarditis: current evidence and future challenges. Front Med. 2017; 4: 78.

45. Maggiolini S, Tiberti G, Cantarini L, Carbone C, Mariani S, Achilli F, et al. Large pericardial effusion in a family with recurrent pericarditis: a report of probable X-linked transmission. Exp Clin Cardiol. 2011; 16: 54-56.

46. Pankuweit S, Wädlich A, Meyer E, Portig I, Hufnagel G, Maisch B. Cytokine activation in pericardial fluids in different forms of pericarditis. Herz. 2000; 25: 748-754.

47. Gamaza-Chulián S, León-Jiménez J, Recuerda-Núñez M, Camacho-Freire S, Gutiérrez-Barrios A, Vargas-Machuca JC. Cardiac troponin-T in acute pericarditis. J Cardiovasc Med. 2014; 15: 68-72.

48. Fabre A, Sheppard MN. Sudden adult death syndrome and other non-ischaemic causes of sudden cardiac death. Heart. 2006; 92: 316-320.

49. Cooper LT. Myocarditis. N Eng J Med. 2009; 360: 1526-1538.

50. Coronado MJ, Bruno KA, Blauwet LA, Tschope C, Cunningham MW, Kytö V, et al. The effects of gender and age on occurrence of clinically suspected myocarditis in adulthood. Heart. 2013; 99: 1681-1684.

51. Cahill TJ, Prendergast BD. Infective endocarditis. Lancet. 2015; 387: 882-893.

52. Breed ER, Binstadt BA. Autoimmune valvular carditis. Curr Allergy Asthma Rep. 2015; 15: 491.

53. Chawla A, Nguyen KD, Goh YS. Macrophage-mediated inflammation in metabolic disease. Nat Rev Immunol. 2011; 11: 738-749.

54. Esser N, Legrand-Poels S, Piette J, Scheen AJ, Paquot N. Infammation as a link between obesity, metabolic syndrome and type 2 diabetes. Diabetes Res Clin Pract. 2014; 105: 141-150.

55. Liu J et al. Genetic deficiency and pharmacological stabilization of mast cells reduce diet-induced obesity and diabetes in mice. Nat Med. 2009; 15: 940-945.

56. Tanaka T, Narazaki M, Ogata A, Kishimoto T. A new era for the treatment of infammatory autoimmune diseases by interleukin-6 blockade strategy. Semin Immunol. 2014; 26: 88-96.

57. Tanaka T, Narazaki M, Kishimoto T. Therapeutic targeting of the interleukin-6 receptor. Annu Rev Pharmacol Toxicol. 2002; 52: 199-219.

58. Waetzig GH, Rose-John S. Hitting a complex target: an update on interleukin-6 trans-signalling. Expert Opin Ther Targets. 2015; 16: 225-236.

59. Rose-John S. IL-6 trans-signaling via the soluble IL-6 receptor: importance for the pro-inflammatory activities of IL-6. Int J Biol Sci. 2012; 8: 1237-1247.

60. Ogata A, Morishima A, Hirano T, Hishitani Y, Hagihara K, Shima Y, et al Improvement of HbA1c during treatment with humanized anti-interleukin 6 receptor antibody, tocilizumab. Ann Rheum Dis. 2010; 70: 1164-1165.

61. Schultz O, Oberhauser F, Saech J, Rubbert-Roth A, Hahn M, Krone W, et al. Effects of inhibition

of interleukin-6 signaling on insulin sensitivity and lipoprotein (a) levels in human subjects with rheumatoid diseases. PLoS ONE. 2010; 5: e14328.

62. Kraakman MJ, Kammoun HL, Allen TL, Deswaerte V, Henstridge DC, Estevez E, et al. Blocking IL-6 trans-signaling prevents high-fat diet-induced adipose tissue macrophage recruitment but does not improve insulin resistance. Cell Metab. 2015; 21: 403-416.

63. Schuett H, Oestreich R, Waetzig HG, Annema W, Luchtefeld M, Hillmer A, et al. Transsignaling of interleukin-6 crucially contributes to atherosclerosis in mice. Arterioscler Thromb Vasc Biol. 2012; 32: 281-290.

64. Larsen CM, Faulenbach M, Vaag A, Vould A, Ehses JA, Seifert B, et al. Interleukin-1-receptor antagonist in type 2 diabetes mellitus. N Engl J Med. 2007; 356: 1517-1526.

65. Van Asseldonk EJP, Stienstra R, Koenen TB, Joosten LAB, Netea MG, Tack CJ. Treatment with anakinra improves disposition index but not insulin sensitivity in nondiabetic subjects with the metabolic syndrome: a randomized, double-blind, placebo-controlled study. J Clin Endocrinol Metab. 2011; 96: 2119-2126.

66. Van Poppel PC, van Asseldonk EJ, et al. The interleukin-1 receptor antagonist anakinra improves first-phase insulin secretion and insulinogenic index in subjects with impaired glucose tolerance. Diabetes Obes Metab. 2014; 16: 1269-1273.

67. Roell MK, Issafras H, Bauer RJ, et al. Kinetic approach to pathway attenuation using XOMA 052, a regulatory therapeutic antibody that modulates interleukin-1beta activity. J Biol Chem. 2010; 285: 20607-20614.

68. Cavelti-Weder C, Babians-Brunner A, Keller C et al. Effects of gevokizumab on glycemia and inflammatory markers in type 2 diabetes. Diabetes Care. 2012; 35: 1654-1662.

69. Rissanen A, Howard CP, Botha J, et al. Effect of anti-IL-1β antibody (canakinumab) on insulin secretion rates in impaired glucose tolerance or type 2 diabetes: results of a randomized, placebocontrolled trial. Diabetes Obes Metab. 2012; 14: 1088-1096.

Citation: Rafik Ragheb. IL-6 as a surrogate biomarker in Inflammatory Heart Disease: cytokines role in the pathogenesis of cardiovascular diseases. SunKrist Endocrinol and Metab Res J. 2021; 2: 1008.