



Analysis of Interleukin-6 in Cardiac and Non-Cardiac Post-Menopausal Women

Priyanka Kumari Mandia¹, P Satyanarayana¹

¹Department of Biochemistry, Pacific Institute of Medical Sciences,
Sai Tirupati University, Udaipur, Rajasthan, India

***Corresponding Author:**

Priyanka Kumari Mandia

Ph.D. Scholar, Department of Biochemistry, Pacific Institute of Medical Sciences,
Sai Tirupati University, Udaipur, Rajasthan, India

Type of Publication: Original Research Paper

Conflicts of Interest: Nil

Abstract

Background: The primary cause of cardiovascular illnesses, atherosclerosis, is largely caused by the interleukin-6 (IL-6) pathway. Our goal was to evaluate the prognostic power of inflammatory biomarkers for long-term cardiovascular death in patients having percutaneous coronary intervention (PCI) who have acute coronary syndrome (ACS) with post menopause .

Methods: This paper focuses on analyzing the importance of biochemical parameters in post-menopausal heart disease including Interleukin -6 and their implications in the evolution of the disease by using standard procedure of selected biochemical parameters.

Results: The present study showed that the value of Interlukin-6 was significantly high in post-menopausal heart disease patient compare to normal patients.

Conclusions: Our study also shows that post-menopausal heart disease patient patient have a high risk of critical condition, heart attack and developing sever disease and also show poor prognosis compared normal patent.

Keywords: IL-6, MT, PMHD

Introduction

For women, cardiovascular disease (CVD) is the main cause of death. [1]. Based on statistics from the Women's Heart Alliance survey conducted in 2017 with 1011 US women aged 25 to 60, and the American Heart Association's 2012 survey on female awareness, knowledge, and perceptions on CVD. [2], only 56% of women are aware of this fact. [3].

CVD and Menopause:

Men are more likely to get coronary heart disease (CHD) than women, and women are more likely to acquire CHD throughout midlife, which is also the time when menopause transitions (MT). The suggestion that the MT adds to the rise in this risk was prompted by this observation. [4].

Longitudinal studies of women going through menopause over the past 20 years have made significant contributions to our understanding of the connection between the MT and CVD risk. Along with negative changes in body fat distribution, lipids, and lipoproteins, these studies have also shown clear patterns of altered endogenous sex hormones and structural and functional indicators of vascular health across the MT. [5] The published results highlight the MT as a period of rapidly increasing CVD risk, which highlights the relevance of midlife monitoring and possible intervention.

Epidemiology of Menopause

Menopause marks the end of ovarian function permanently and the shift in women's life cycles from

one of reproduction to nonreproduction. It denotes a crucial phase marked by striking adjustments to menstrual and hormonal rhythms, along with physical and psychological problems.

Natural menopause is defined as the occurrence of amenorrhea for 12 consecutive months, independent of external factors. A 2018 study that combined data from 17 cross-sectional and observational studies with 234 811 postmenopausal women from 7 different countries revealed that the median age of natural menopause was 50.0 years (interquartile range: 48.0–53.0 years).[6]. When a woman experiences her natural menopause, it is deemed premature if it happens before the age of 40 and early if it happens between the ages of 40 and 45.9. 10% of women go through menopause before the age of 45 (1.9% before the age of 40 and 7.3% between the ages of 40 and 45).[6]. Given that a US woman's mean life expectancy at birth is 81 years, many of these women will spend as much as 40 percent of their lives as postmenopausal. [7,8]

It is thought that the proper amount of endogenous estrogen released throughout the menstrual cycle has a cardioprotective impact on premenopausal women. This may be the cause of fertile women's lower incidence of coronary heart disease than that of males [9]. But as a person reaches menopause, their ovaries stop producing a considerable quantity of estrogen, making them more vulnerable to conditions like osteoporosis, dyslipidemia, and heart disease that are linked to low estrogen levels [10, 11]. Following menopause, there are major hormonal changes that impact plasma lipid and lipoprotein metabolism, ultimately leading to cardiac-related diseases. These changes include reduced plasma estrogen levels and higher levels of luteinizing hormone (LH) and follicle stimulating hormone (FSH) [12, 13].

By preserving low levels of TAG and LDL-C and high levels of HDL-C, estrogen has a cardioprotective impact. Increased expression of LDL receptors on cell surfaces and an accelerated conversion of hepatic cholesterol to bile acids are likely the causes of the mass clearance of LDL-C from the plasma. HDL-C is made more abundant when apolipoprotein A-I is produced more and hepatic lipase activity is reduced [14].

Such cardio defensive effect is lost after menopause driving postmenopausal women towards high risk of

debilitating and often fatal complications of cardiovascular disease (CVD) [15].

According to American Heart Association report (2002), after menopause 70% of women develop cardiovascular disease and 30% develop osteoporosis in USA [11].

Materials And Methods

A study was conducted in Pacific Institute of Medical Sciences, Rajasthan, from March 2019 to December 2021 on Post Menopause with cardiovascular disease patient. The source population was all cases of cardiovascular disease admitted at PIMS with a confirmed diagnosis of cardiac disease reported by central laboratory and cardiology department.

A total number of 100 patients admitted at Pacific Institute of Medical Sciences Udaipur, was form the subjects of the present study. Out of these 50 patients were suffering from heart disease, and 50 were normal patients. Efforts will be made to match all anthropometric factors comparable to both the groups of patients.

Group 1: Confirm post-menopausal 50-70 years' healthy women patients.

Group 2: Confirm post-menopausal women with coronary heart disease age 50-70 years.

Inclusion Criteria

1. Patient who are willing to participate.
2. Post-menopausal women with coronary heart disease diagnosed by cardiology department.

Exclusion Criteria: -

1. Patients below 50 years and above 70 years of age will be excluded in the study.
2. The individuals with metabolic diseases, malnutrition, or histories of consuming vitamins or minerals supplements, regular steroids will be excluded from the study.
3. Diagnosed cancer patients will be excluded.
4. Individuals with Diabetes mellitus, liver diseases, kidney disease, rheumatoid arthritis, patients will be excluded.
5. To minimize the effect of life style on lipid profile trained athletes or sports women will be excluded from the study.

6. Post-menopausal women with thyroid dysfunction and those who are taking antihypertensive drug will be excluded

Clinical Methodology: Serum Interlukin -6 was recorded by using Autoanalyzer Maglumi 2000 plus

Statistical Analysis: For the quantitative analysis, we used the software SPSS software. In this meta-analysis, all p values reported were two-tailed with the statistical significance set at ≤ 0.05 .

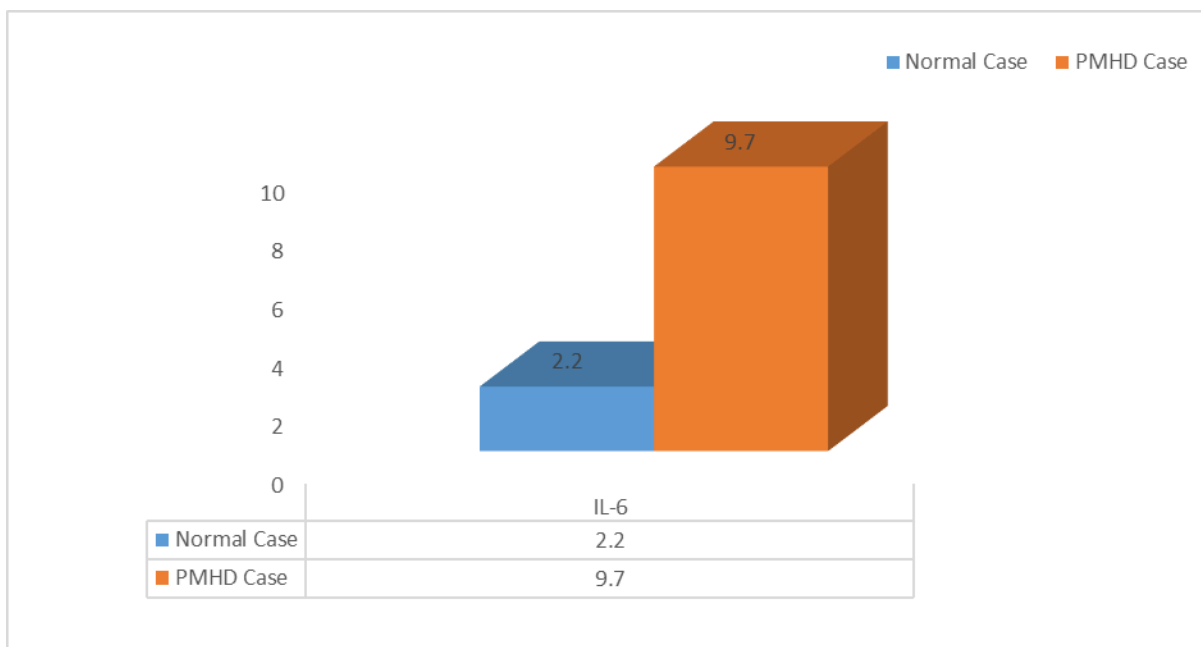
Result

The present study showed that the mean value and standard deviation of Interleukin -6 (9.7 ± 6.2) was significantly high in post menopause cardiac women with P value (< 0.0001) compare to normal women with post menopause (2.2 ± 0.74). (Shown in Table .1 and Figure.1).

Table 1: Comparison of Interleukin -6 between Normal Patient and post-menopausal heart disease patients

S.No	Test	Normal Patient		Pmhd Cases		P Value
		Mean	SD	Mean	SD	
1	IL-6	2.20	0.74	9.7	6.2	$P < 0.0001$

Fig 1: Comparison of Interleukin -6 between Normal Patient and post-menopausal heart disease patients



Discussion

The present study showed that the mean value and standard deviation of Interleukin -6 (9.7 ± 6.2) was significantly high in post menopause cardiac women with P value (< 0.0001) compare to normal women with post menopause (2.2 ± 0.74).

And this study also showed that the post-menopausal women had an increased hazard to die from heart attack after menopause.

Numerous studies have previously documented the connection between elevated blood IL-6 and postmenopausal cardiovascular diseases (CVD) [16,17,18–20]. For example, prior studies have demonstrated that individuals with IL-6

concentrations more than 1 pg/mL had higher incidences of CAD than patients with lower IL-6 values [21]. The link between elevated concentrations of IL-6 and an increased risk of cardiovascular death throughout a mean follow-up duration of 7 years in persons without documented CVD at study entrance was again underlined by a recent meta-analysis synthesizing 11 studies [22].

Moreover, there is a correlation between increased IL-6 and CVD and higher rates of both cardiovascular and all-cause mortality [23]. In an aged population, the MEMO study evaluated several cytokines (IL-1beta, IL-4sR, IL-6, IL-8, IL-10, IL-12, TNF-alpha), and it showed that only IL-6 was consistently linked to death, regardless of the tertile (lower, middle, and upper) and correction. Notably, these results were restricted to men [24].

The Women's Health and Aging Study, however, also provided evidence in favor of the relationships between IL-6 levels and mortality in older, handicapped women with common CVD [25]. Increased IL-6 levels were found to be strongly correlated with the occurrence of adverse events (such as MACE, cardiovascular and all-cause mortality, and cancer mortality) in patients with stable coronary heart disease, according to data from the STABILITY trial [26]. A comparable set of findings was observed in another study, which reported that individuals with stable angina who had IL-6 concentrations ≥ 3.67 pg/mL were three times more likely to suffer cardiovascular events over a mean follow-up period of 6.3 years [27].

Conclusion

The present study done on Normal patient and post menopause heart disease patient admitted in Pacific Institute of Medical Sciences, Umarda, Udaipur. Total 100 patients were included for this study .50 was normal patient and 50 was post menopause heart disease patient. 50-70 age group was taken for this study. Present study showed that the mean value and standard deviation of Interleukin -6 (9.7 ± 6.2) was significantly high in post menopause cardiac women with P value (< 0.0001) compare to normal women with post menopause (2.2 ± 0.74).

And this study also showed that the post-menopausal women had an increased hazard to die from heart attack after menopause.

Ethical Issues

Research project approved by the ethics committee of Pacific Institute of Medical Sciences, Umarda Udaipur- 313005, Rajasthan, INDIA.

References

1. Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP, Chamberlain AM, Chang AR, Cheng S, Das SR, et al; on behalf of the American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2019 update: a report from the American Heart Association [published correction appears in *Circulation*. 2020;141:e33]. *Circulation*. 2019;139:e56–e528. doi: 10.1161/CIR.0000000000000659
2. Mosca L, Hammond G, Mochari-Greenberger H, Towfighi A, Albert MA; on behalf of the American Heart Association Cardiovascular Disease and Stroke in Women and Special Populations Committee of the Council on Clinical Cardiology, Council on Epidemiology and Prevention, Council on Cardiovascular Nursing, Council on High Blood Pressure Research, and Council on Nutrition, Physical Activity and Metabolism. Fifteen-year trends in awareness of heart disease in women: results of a 2012 American Heart Association national survey. *Circulation*. 2013;127:1254–1263, e1. doi: 10.1161/CIR.0b013e318287cf2f
3. Bairey Merz CN, Andersen H, Sprague E, Burns A, Keida M, Walsh MN, Greenberger P, Campbell S, Pollin I, McCullough C, et al. Knowledge, attitudes, and beliefs regarding cardiovascular disease in women: the Women's Heart Alliance. *J Am Coll Cardiol*. 2017;70:123–132. doi: 10.1016/j.jacc.2017.05.024
4. Kannel WB, Hjortland MC, McNamara PM, Gordon T. Menopause and risk of cardiovascular disease: the Framingham study. *Ann Intern Med*. 1976;85:447–452. doi: 10.7326/0003-4819-85-4-447
5. El Khoudary SR. Gaps, limitations and new insights on endogenous estrogen and follicle stimulating hormone as related to risk of

- cardiovascular disease in women traversing the menopause: a narrative review. *Maturitas*. 2017;104:44–53. doi: 10.1016/j.maturitas.2017.08.003
6. WHO Scientific Group on Research on the Menopause. Research on the menopause in the 1990s: report of a WHO scientific group. World Health Organ Technical Report Series. 1996;866:1–107.
 7. Santoro N, El Khoudary SR, Sokalska A, Szmuiłowicz ED, Wolfman W. Menopause. In: *Menopause Practice: A Clinician’s Guide*. Pepper Pike, OH: The North American Menopause Society; 2019:1–21.
 8. Kochanek KD, Murphy SL, Xu J, Tejada-Vera B. Deaths: final data for 2014. *Natl Vital Stat Rep*. 2016;65:1–122.
 9. Mendelsohn M. E., Karas R. H. The protective effects of estrogen on the cardiovascular system. *The New England Journal of Medicine*. 1999;340(23):1801–1811. doi: 10.1056/NEJM199906103402306. [PubMed] [CrossRef] [Google Scholar]
 10. Reddy Kilim S., Rao Chandala S. A comparative study of lipid profile and oestradiol in pre- and post-menopausal women. *Journal of Clinical and Diagnostic Research*. 2013;7(8):1596–1598. doi: 10.7860/JCDR/2013/6162.3234. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
 11. Kumar S., Shah C. Oommen ER study of cardiovascular risk factors in pre and postmenopausal women. *International Journal of Pharma Sciences and Research*. 2012;3(12):560–570. [Google Scholar]
 12. Deepthi S., Naidu J., Narayan A. R. Relationship between estrogen and lipid profile status in postmenopausal women. *International Journal of Applied Biology and Pharmaceutical Technology*. 2012;3(3):230–234. [Google Scholar]
 13. Varu D. M. S., Vegad D. A. M., Jani D. H. A., Savalia D. C. V., Joshi D. V. S. A comparative study of serum lipid profile between premenopausal and postmenopausal women. *National Journal of Integrated Research in Medicine*. 2012;3(1):43–45. [Google Scholar]
 14. Guetta V., Cannon R. O., III Cardiovascular effects of estrogen and lipid-lowering therapies in postmenopausal women. *Circulation*. 1996;93(10):1928–1937. doi: 10.1161/01.CIR.93.10.1928. [PubMed] [CrossRef] [Google Scholar]
 15. Pardhe BD, Ghimire S, Shakya J, Pathak S, Shakya S, Bhetwal A, et al. Elevated cardiovascular risks among postmenopausal women: A community based case control study from Nepal. *Biochem Res Int* [Internet]. 2017;2017:1–5. Available from: <http://dx.doi.org/10.1155/2017/3824903>
 16. B.C. Bacchiega, A.B. Bacchiega, M.J.G. Usnayo, R. Bedirian, G. Singh, GdRC Pinheiro, Interleukin 6 inhibition and coronary artery disease in a high-risk population: a prospective community-based clinical study, *J. Am. Heart Assoc*. 6 (3) (2017) e005038.
 17. E. Lindmark, E. Diderholm, L. Wallentin, A. Siegbahn, Relationship between interleukin 6 and mortality in patients with unstable coronary artery disease: effects of an early invasive or noninvasive strategy, *Jama* 286 (17) (2001) 2107–2113.
 18. Y. Hongmei, J. Yongping, L. Jiyuan, Interleukin-6 polymorphisms and risk of coronary artery diseases in a Chinese population: a case-control study, *Pak. J. Med. Sci*. 32 (4) (2016) 880.
 19. Collaboration IRGCERF, Interleukin-6 receptor pathways in coronary heart disease: a collaborative meta-analysis of 82 studies, *Lancet* 379 (9822) (2012) 1205–1213.
 20. H. Hou, C. Wang, F. Sun, L. Zhao, A. Dun, Z. Sun, Association of interleukin-6 gene polymorphism with coronary artery disease: an updated systematic review and cumulative meta-analysis, *Inflamm. Res*. 64 (9) (2015) 707–720.
 21. M.V. Wainstein, M. Mossmann, G.N. Araujo, S.C. Gonçalves, G.L. Gravina, M. Sangalli, F. Veadrigo, R. Matte, R. Reich, F.G. Costa, Elevated serum interleukin6 is predictive of coronary artery disease in intermediate risk overweight patients referred for coronary angiography, *Diabetol. Metab. Syndr*. 9 (1) (2017) 67.

22. B. Zhang, X.L. Li, C.R. Zhao, C.L. Pan, Z. Zhang, Interleukin-6 as a predictor of the risk of cardiovascular disease: a meta-analysis of prospective epidemiological studies, *Immunol. Investig.* 47 (7) (2018) 689–699.
23. D. Su, Z. Li, X. Li, Y. Chen, Y. Zhang, D. Ding, X. Deng, M. Xia, J. Qiu, W. Ling, Association between serum interleukin-6 concentration and mortality in patients with coronary artery disease, *Mediat. Inflamm.* 2013 (2013).
24. B.T. Baune, M. Rothermundt, K.H. Ladwig, C. Meisinger, K. Berger, Systemic inflammation (Interleukin 6) predicts all-cause mortality in men: results from a 9-year follow-up of the MEMO Study, *Age* 33 (2) (2011) 209–217.
25. S. Volpato, J.M. Guralnik, L. Ferrucci, J. Balfour, P. Chaves, L.P. Fried, T.B. Harris, Cardiovascular disease, interleukin-6, and risk of mortality in older women: the women's health and aging study, *Circulation* 103 (7) (2001) 947–953.
26. C. Held, H.D. White, R.A. Stewart, A. Budaj, C.P. Cannon, J.S. Hochman, W. Koenig, A. Siegbahn, P.G. Steg, J. Soffer, Inflammatory biomarkers interleukin-6 and Creactive protein and outcomes in stable coronary heart disease: experiences from the STABILITY (stabilization of atherosclerotic plaque by initiation of darapladib therapy) trial, *J. Am. Heart Assoc.* 6 (10) (2017) e005077
27. E.Z. Fisman, M. Benderly, R.J. Esper, S. Behar, V. Boyko, Y. Adler, D. Tanne, Z. Matas, A. Tenenbaum, Interleukin-6 and the risk of future cardiovascular events in patients with angina pectoris and/or healed myocardial infarction, *Am. J. Cardiol.* 98 (1) (2006) 14–18.