Effect of highly sensitive C-reactive protein on cardiovascular risk of Type 2 diabetes mellitus adults: A systematic review

Benoy Upreti[1], Mingma Lhamu Sherpa[2], Karma Lakhi Bhutia[3]

[1]Assistant Professor, [2]Professor and Head, Department of Biochemistry, [3]Assistant Professor, Department of Anatomy, Sikkim Manipal Institute of Medical Sciences, Gangtok, Sikkim, India

ABSTRACT

Diabetes mellitus (DM) is a significant global health issue that affects nearly 537 million of people, with Type 2 DM (T2DM) accounting for the majority of cases. Death is frequently the result of diabetes-related complications, particularly cardiovascular illnesses, neuropathy, retinopathy, and nephropathy. Type 2 diabetes and cardiovascular events, such as coronary heart disease (CHD), are linked to a greater likelihood of creating when C-reactive protein (CRP), a representative acute phase inflammation response protein, is elevated. The purpose of this systematic review is to examine how T2DM adults' cardiovascular risk is affected by highly sensitive CRP (hsCRP). The information found through searches of digital sources such as EBSCO, EMBASE, PubMed, Scopus, and Web of Science. The investigator separately reviewed each abstract and title in comparison to predetermined inclusion and exclusion standards. Google Scholar was used for further research. Using terms, a thorough search plan was created. The terms "hs-CRP," "Type 2 diabetes mellitus," and "cardiovascular disease" have been utilized. To translate the results for other databases, the original search was done in PubMed. To find additional pertinent papers, reference lists of the research included and previously released reviews were also examined. The findings state that people with DM have a higher risk of developing heart disease. Due to their elevated carbohydrate intake, unhealthy diet, and genetic disposition, Asian Indians are at a high risk of developing cardiovascular disease and DM. Diabetes patients' cardiovascular risk is primarily determined by insulin sensitivity, which can be assessed using the markers hsCRP and tumor necrosis factor-. Lipid profile is important in cardiovascular diseases because high blood glucose levels encourage the body's production of cholesterol, which increases the risk of heart malfunction in obese diabetic patients.

Key words: Diabetes mellitus; Metabolic disease; Cardio vascular disease

INTRODUCTION

Diabetes mellitus (DM) is a rising global metabolic disease that is instigating other complications in the human body leading to major consequences. It is characterized by elevated glucose levels resulting from defects in insulin secretion or action.[1,2] DM is a major global health problem affecting approximately 537 million people according to International Diabetes Federation (2021). By 2045, this number is expected to increase to 784 million. Approximately 90–95% of these cases are Type 2 DM (T2DM).[3-5] DM is a devastating disease. The estimated 5-year mortality rate in patients with T2DM is calculated as 18.9%. Diabetic complications, mainly cardiovascular diseases[6-8] neuropathy,[9,10] retinopathy,[11,12] and nephropathy[13,14] with subsequent amputation,[15,16] usually lead to death.[17-20]

CRP is a representative acute phase inflammation response protein. It is mainly synthesized in the liver, stimulated by inflammatory cytokines such as interleukin-6, and has a half-life of up to 19 h.[21] With the advancement of technology, a high sensitivity (Hs)-CRP assessment method was developed, enabling the measurement of

Address for Correspondence:
Dr. Benoy Upreti, Assistant Professor, Department of Biochemistry, Sikkim Manipal Institute of Medical Sciences, Gangtok, Sikkim, India.
Mobile: +91-9933090092. **E-mail:** bnyooyup@gmail.com

CRP with high precision even at low concentration, or mild elevation such as that seen in chronic inflammation.[22] CRP is linked to a higher risk of getting Type 2 diabetes (T2D), according to a number of prospective cohort research investigations and nested case–control research.[23] Inconclusive findings were found in certain investigations that looked at the connection between HbA1c and Hs-CRP in diabetic patients.[24] Chronic CRP increase could additionally have biological impacts on atherosclerotic plaque stability, low-density lipoprotein (LDL) oxidation, fibrinolysis, coagulation, and endothelial function.[25] According to numerous investigations, elevated levels of CRP are linked to a greater risk of cardiovascular incidents, including CHD.[26] The American Heart Association has determined that Hs-CRP amounts influence cardiovascular risk.[27] According to the study, CRP in the human body is highly related with the cardiovascular risks is also tested for understanding the insulin level in blood which causes major harm to the heart.[28] The total relative risk of T2D was 1.26 (95% confidence interval 1.16–1.37) per increase of 1 log mg/L in CRP levels, according to a meta-analysis of 18 prospective research investigations.[23] However, to the best of our knowledge, there is no single study that discusses the effect of hsCRP on cardiovascular risk of T2DM adults. In terms of dietary regulations, this study is highly significant to aware people about the nutrition aspect of diabetes patients.

Aims and objectives

To evaluate association of glycated albumin, hs-CRP with risk of developing cardiovascular complications among type 2 DM patients.

MATERIALS AND METHODS

Search strategy

This systematic review was prepared in accordance with the preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines.[29] For data extraction, data synthesis, and meta-analysis, standard techniques should be taken into account. In addition, the participants, interventions, comparisons, and outcomes strategy was modified according to the review's population, exposure, and outcome.

Study design

The review contains studies using observation that concentrate on the extremely responsive CRP on cardiovascular risk of T2DM, which include cross-sectional research and subsequent research. In the study selection process for research, the inclusion and exclusion criteria play an important role. The study for the systemic review has been selected based on some criteria. Those studies

are selected for the systematic reviews which are written in English. Those studies are also selected for the systematic review in the present study which are available in the proper PDF format and which has page and volume number. On the other hand, some scholarly articles are also selected which have relevant information related to the subject matter of the present study. The following were excluded from the study: opinions, case reports/series, systematic reviews, proceedings from conferences, narrative reviews, commentaries, and letters to the editor.

Population (P): Adults with T2DM

Intervention (I): hs-CRP measurement

Comparison (C): Participants who had high levels of hs-CRP in comparison to those who had low levels

Result (O): Risk factors for cardiovascular disease, including mortality, myocardial infarction, stroke, and peripheral artery disease, can be used to quantify this risk.

Study selection

The information was found through searches of digital sources such as EBSCO, EMBASE, PubMed, Scopus, and Web of Science. The investigator separately reviewed each abstract and title in comparison to predetermined inclusion and exclusion standards. Google Scholar was used for further research. Using terms, a thorough search plan was created. The terms "hs-CRP," "Type 2 diabetes mellitus," and "cardiovascular disease" have been utilized. To translate the results for other databases, the original search was done in PubMed. To find additional pertinent papers, reference lists of the research included and previously released reviews were also examined.

Data extraction and quality assessment

For the extraction of data, the research papers that had been selected at the full-text step were carried over. Data are gathered, and the details pertaining to the topic are interpreted. The research papers were carefully chosen to ensure the caliber of the study. From the papers that are specifically focused on the topic, only pertinent information is taken. Existing journals that contain peer-reviewed articles about medical issues are gathered as secondary data for this research. A systematic evaluation is carried out to assess the results. The criteria for choosing and the number of papers utilized in this research are presented in a flow chart using the PRISMA table. The following information was taken out of the research: (a) creator and article information, (b) region or country, (c) objective of the study, (d) methodology employed, (e) participant and population sub-group demographic information, (f) additional primary results, and (g) conclusion.

Author	Study design	country	Findings	Significance	Participants	Duration
Kamath et al.[30]	Parallel	India	CVD are common among diabetes patients who have a past history of hs-CRP. Inflammation in the blood causes acute coronary syndrome, peripheral artery disease, and stroke. CRP levels in the human body are stable as they do not react to the intake of food. hsCRP has some properties that influence the endothelial dysfunction in the human body, which causes cardiovascular disease among diabetes mellitus patients in India.	This study aims to evaluate the significance of hsCRP in the occurrence of CVD among diabetes mellitus patients. The relevance of hsCRP and CRP among different regional people is also investigated, indicating the accuracy of the cardiovascular disease chances making humans prone to get inflammation in the blood.	Patients with low grade of systematic inflammation and normal cholesterol level.	Past two decades.
Mohan et al.[31]	Cross-sectional and longitudinal	Asia-India	Glycated albumin is triggered by the dietetic factors of humans, and cardiovascular disorders among diabetes patients are directly relevant to dietary factors. The dietary factors of Asian people include carbohydrates in different forms that increase the chances of diabetes. Inclusion of refined substances in the daily diet triggers inflammation in blood, which is the main reason for diabetes as basal stability gets interrupted from higher intake of glucose and carbohydrate. Higher glucose level or blood sugar in blood limits the functions of blood vessels	This study aims to identify the relevance of albumin in measuring the fructose level in the human body, which generates from glucose intake. Carbohydrate is a major source of glucose in the human body; hence the dietary factors were found to be extremely relevant and impactful on CVD control.	Patients with MS and cardiovascular disease	Not specified
Khare et al.[32]	Parallel	India	Diabetes mellitus can cause chronic COPD. COPD restricts the blood flow in the heart leading to major consequences for people. Inflammation in the lungs is caused mainly from smoking and inhalation of harmful substances which restrict the flow of blood in the heart. Increasing blood sugar level in the human body limits the normal function of the lungs, which causes COPD among diabetes patients. Endothelial function among COPD patients causes major issues in the lungs which causes damage in the vasodilatory function leading to major cardiovascular risk among the patients.	This study aims to develop the relativity between the lungs' condition and the CVD by identifying the underlying causes of COPD, which is an inflammatory disease in the lungs that restricts the normal functions of lungs.	16 COPD patients	3 min
Indumathy et al.[33]	Parallel	India	Insulin resistance is a major concern among diabetes patients who possess a higher risk of cardiovascular disease as cardiometabolic risks increase with an imbalance in the insulin level in the human body. Cardiovascular risk among insulin-resistance groups is higher compared to non-insulin-resistant people. Obesity among diabetic patients determines the insulin resistance level.	This study aims to evaluate the relationship between insulin resistance and cardiovascular risk among diabetic patients.	Obese individuals	2012–2015

(Contd...)

Author	Study design	country	Findings	Significance	Participants	Duration
Enas et al.[34]	Parallel	Asia-India	Early CVD are becoming common throughout the world and Statin is a major therapy for reducing the cardiovascular disease mortality especially among people who have high lipid profile. CVD is the major cause of deaths among the global population and India has the highest rate of mortality among developing countries.[5] Atherosclerosis and cholesterol are the major drivers of cardiac arrest among certain populations. saturated fat intake instead of polyunsaturated fat among the population increases cholesterol in blood and the relativity of CVD and cholesterol is extremely widespread. LDL causes fatal conditions among chronic kidney disease patients as it is the main cause of fat build-up in blood from cholesterol. Reducing the LDL in is a major part of statin therapy which targets to restrict the growth of coronary atherosclerosis. It has been observed in the study that people with high lipoprotein in blood possess comparatively higher risk of CVD than the rest of the population. Hence, statin therapy targets to reduce the lipid level in the body.	Through this study a strong understanding of LDL is developed which is causing the majority of deaths among India's young population. Rising CVD risk throughout the globe is identified which gives an insight on the statin therapy emergence as a popular treatment for reducing the CVD risk among diabetes mellitus patients. Importance of early intervention with statin therapy is acknowledged through this study which can be used for awareness.	Patients with cardiovascular disease.	

hs-CRP: High-sensitivity C-reactive protein, COPD: Obstructive pulmonary disease, LDL: Low-density lipoprotein, CVD: Cardiovascular diseases

Data analysis and synthesis

Obtained data are analyzed using a systematic review method where each article was discussed with their core findings. Each article is contributing to generating a critical analysis on the relevant factors. Using the systematic review method each article was thoroughly explored and only factual information was selected including survey results and descriptive knowledge.

Outcome measures

Increasing rate of DM and cardiovascular disease is becoming a global concern, hence, through this study a clear understanding of cardiovascular diseases among diabetes patients is expected. Outcome of this study is to determine the hsCRP role in controlling the cardiovascular risk in DM patients.

RESULTS

Flow of studies

The researcher of the present study has selected 50 articles for the systematic reviews and entire data analysis. Only five studies among those are selected because others are not meeting the inclusion criteria. Two studies among 50 articles were not in the English language and others were not informative enough regarding the subject matter of the

present research. Scanning of abstracts removed 20 articles and their meaning 28 articles were tested for eligibility and only 10 articles were found to be appropriate. Based on relevance and accuracy, three more articles were removed. Two articles are used which are published in 2013 and 2015 and the rest in 2018.

Study characteristics

The characteristics of the studies are briefly seen in the systematic reviews. All the studies which are selected for the systematic review are published between 2013 and 2018. The selected five studies were conducted in India. The selected trials assessed the effect of the intervention among patients with diabetes, blood pressure variability, and obese individuals.

DISCUSSION

Carbohydrate quality matters in cardiovascular diseases as the study results suggest that chronic complications of diabetes are the main reason for cerebrovascular and macroangiopathy disease. Glycemic index, protein, and carbohydrate type in the diet of the participants are tested which indicates that Type 2 diabetes is triggered by the level of the glycaemic index in the body. The inclusion of whole grains provides fibre in the body which reduces systolic

blood pressure leading to a low risk of CHD. glycaemic properties are improved with a high-fiber wheat diet which eliminates the risk of T2D patients getting heart diseases. Whereas energy generated from fat decreases the chances of mortality among T2D patients. Cardiovascular diseases among T2DM patients require a proper test of CRP to determine the level of inflammation in the lungs. The function of endothelium and inflammation can increase the risk of cardiovascular disease among COPD patients.

The body mass index (BMI) of a diabetes patient is highly impactful on the vascular system and COPD patients have higher chances of heart disease if their BMI is high. Obese people suffer from improper BMI rates which increases their chances of being affected in the lungs, leading to major heart conditions.[32] T2DM patients who are obese have shown a higher rate of COPD. Cardiovascular diseases are frequent in insulin resistance (IR) people as the blood flow in their heart is highly unstable as the blood sugar is high in the blood which is not being used by the cells. The high blood sugar level in blood facilitates IR among people which limits the blood flow in the heart causing major heart diseases which can be fatal in obese people.

Among the insulin non-resistance group, the chances of cardiovascular diseases have been observed to be less compared to the IR group as the blood sugar is properly being utilized by body cells. Thus, it is clear that to reduce the chances of cardiovascular diseases it is important to control the insulin level, lipid profile, and BMI. Adiponectin can be used to treat obesity and insulin imbalance. However, a lack of circulatory adiponectin in the body imposes a greater risk of cardiovascular diseases among IR patients and a surge of serum neopterin can make the cardiovascular system unfavorable for diabetic patients. Baroreceptor sensitivity must be controlled in Insulin-resistant patients to reduce the chances of morbidity of cardiovascular conditions.[32] IR is the major driver of cardiovascular diseases in obese and non-obese groups which refers to the fact that diabetic patients have higher chances of being affected by cardiovascular disease. Pre-obese period and post-obese period both include the risks of cardiovascular conditions among diabetes patients if the Insulin level is not within the desired level.

Hence, precautionary measures must be taken to remove the vulnerabilities of cardiovascular diseases among T2DM patients. In addition, Asian people especially the Indian population have excessive IR which makes them more exposed to cardiovascular diseases.[33] In addition, Elevated triglycerides are controlled by statin therapies which are caused by IR and obesity. Fatality rates of cardiovascular diseases are mostly found among individuals who have DM. Asian Indians have a higher rate of DM and low tolerance to glucose even after maintaining their obesity level. High lipid profile among young Asian Indians is the main reason for early cardiac arrest and by reducing the LDL, Statin therapy aims to reduce the risk of cardiovascular diseases among young people. Early adoption of Statin therapy has represented a lower mortality rate from coronary artery disease (CAD). Atherosclerosis in children is developed from high cholesterol which affects Indians as they grow old. Cardiovascular disease is observed to affect these kinds of individuals at an early age as their LDL develops atherosclerotic leading to early death.

Children with diabetes must be intervened at earliest as possible to reduce their chances of cardiovascular diseases as reduction of LDL is more effective at an early age compared to the later period when atherosclerosis develops strongly. Global CAD burden can be reduced by treating diabetes patients at the right time with statin therapy. Asian Indians are genetically prone to have higher lipid levels in their blood and the adaptability of unhealthy lifestyles among them increases their vulnerability to diabetes at an early age.[34] Statin therapy can have adverse effects if diabetes patients have other health conditions such as cancer. Medication can interfere with the treatment of an individual by interrupting the functions of different organs. Despite this, statin therapy eliminates the chances of mortality risk among DM patients as a primary preventive measure. Reduction of LDL is the main aim of statin therapy as higher CRP levels and cholesterol can infuse the risk of diabetes patients having cardiovascular diseases at an early age.

CONCLUSION

It has been observed from the systematic review that DM patients have higher chances of being affected from cardiovascular diseases. Asian Indians are at high risk of cardiovascular disease and DM due to their high carbohydrate intake, unhealthy lifestyle, and genetic factors. IR is the major determinant of the cardiovascular risk among diabetes patients which can be tested through hsCRP and tumor necrosis factor-α. Lipid profile matters in cardiovascular diseases as obese diabetic patients have higher chances of heart failure as cholesterol blocks the arteries and high levels of glucose in blood support cholesterol development in the body.

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RECOMMENDATIONS

In future systematic reviews, a diverse range of data sources should be selected to gather optimum knowledge regarding the subject area, restrictions of data collection from specific sources limit the abundance of information. Hence, integrating different medical research sources can expand the quantitative analysis with large samples. Diverse range of sources can provide region-based information, unlike this study where a specific focus has been given to the Asian region.

REFERENCES

1. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2009;32(Suppl 1):S62-S67.
   https://doi.org/10.2337/dc09-S062

2. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2014;37(Suppl 1):S81-S90.
   https://doi.org/10.2337/dc14-S081

3. Ambad R, Jha RK, Chandi DH and Hadke S. Association of leptin in diabetes mellitus and obesity. Res J Pharm Technol. 2020;13(12):6295-6299.
   https://doi.org/10.5958/0974-360X.2020.01095.1

4. Piero MN, Nzaro GM and Njagi JM. Diabetes mellitus-a devastating metabolic disorder. Asian J Biomed Pharm Sci. 2015;4(40):1-7.
   https://doi.org/10.15272/ajbps.v4i40.645

5. Rao US, Zin T, Subramaniam SA, Shan TB, Mogan KA and Ismail AS. Cross-sectional study on knowledge, attitude and practice regarding diabetes mellitus among medical and non-medical students. Res J Pharm Technol. 2018;11(11):4837-4841.
   https://doi.org/10.5958/0974-360X.2018.00879.X

6. Leon BM and Maddox TM. Diabetes and cardiovascular disease: Epidemiology, biological mechanisms, treatment recommendations and future research. World J Diabetes. 2015;6(13):1246-1258.
   https://doi.org/10.4239/wjd.v6.i13.1246

7. Einarson TR, Acs A, Ludwig C and Panton UH. Prevalence of cardiovascular disease in type 2 diabetes: A systematic literature review of scientific evidence from across the world in 2007-2017. Cardiovasc Diabetol. 2018;17(1):83.
   https://doi.org/10.1186/s12933-018-0728-6

8. Ma CX, Ma XN, Guan CH, Li YD, Mauricio D and Fu SB. Cardiovascular disease in type 2 diabetes mellitus: Progress toward personalized management. Cardiovasc Diabetol. 2022;21(1):74.
   https://doi.org/10.1186/s12933-022-01516-6

9. Yagihashi S, Mizukami H and Sugimoto K. Mechanism of diabetic neuropathy: Where are we now and where to go? J Diabetes Investig. 2011;2(1):18-32.
   https://doi.org/10.1111/j.2040-1124.2010.00070.x

10. Feldman EL, Callaghan BC, Pop-Busui R, Zochodne DW, Wright DE, Bennett DL, et al. Diabetic neuropathy. Nat Rev Dis Primers. 2019;5(1):41.
    https://doi.org/10.1038/s41572-019-0092-1

11. Coyne KS, Margolis MK, Kennedy-Martin T, Baker TM, Klein R, Paul MD, et al. The impact of diabetic retinopathy: Perspectives from patient focus groups. Fam Pract. 2004;21(4):447-453.
    https://doi.org/10.1093/fampra/cmh417

12. Nentwich MM and Ulbig MW. Diabetic retinopathy-ocular complications of diabetes mellitus. World J Diabetes. 2015;6(3):489-499.
    https://doi.org/10.4239/wjd.v6.i3.489

13. Lim AK. Diabetic nephropathy-complications and treatment. Int J Nephrol Renovasc Dis. 2014;7:361-381.
    https://doi.org/10.2147/IJNRD.S40172

14. Ruiz-Ortega M, Rodrigues-Diez RR and Lavoz C and Rayego-Mateos S. Special issue "Diabetic nephropathy: Diagnosis, prevention and treatment". J Clin Med. 2020;9(3):813.
    https://doi.org/10.3390/jcm9030813

15. Alvarsson A, Sandgren B, Wendel, Alvarsson M and Brismar K. A retrospective analysis of amputation rates in diabetic patients: Can lower extremity amputations be further prevented? Cardiovasc Diabetol. 2012;11(1):18.
    https://doi.org/10.1186/1475-2840-11-18

16. Mounika V, Sarumathy S, Ebens JA and Shanmugarajan TS. A prospective study on incidence of Anaemia in type 2 diabetes mellitus patients. Res J Pharm Technol. 2017;10(1):11.
    https://doi.org/10.5958/0974-360X.2017.00003.8

17. Cusick M, Meleth AD, Agrón E, Fisher MR, Reed GF, Knatterud GL, et al. Associations of mortality and diabetes complications in patients with type 1 and type 2 diabetes: Early treatment diabetic retinopathy study report no. 27. Diabetes Care. 2005;28(3):617-625.
    https://doi.org/10.2337/diacare.28.3.617

18. Zhu M, Li J, Li Z, Luo W, Dai D, Weaver SR, et al. Mortality rates and the causes of death related to diabetes mellitus in Shanghai Songjiang District: An 11-year retrospective analysis of death certificates. BMC Endocr Disord. 2015;15(1):45.
    https://doi.org/10.1186/s12902-015-0042-1

19. Asfandiyarova NS. Risk factors of death in diabetes mellitus. Klin Med (Mosk). 2016;94(9):697-700.

20. Ling W, Huang Y, Huang YM, Fan RR, Sui Y and Zhao HL. Global trend of diabetes mortality attributed to vascular complications, 2000-2016. Cardiovasc Diabetol. 2020;19(1):182.
    https://doi.org/10.1186/s12933-020-01159-5

21. Seo YH and Shin HY. Relationship between hs-CRP and HbA1c in diabetes mellitus patients: 2015-2017 Korean national health and nutrition examination survey. Chonnam Med J. 2021;57(1):62-67.
    https://doi.org/10.4068/cmj.2021.57.1.62

22. Park JY, Kim MJ and Kim JH. Influence of alcohol consumption on the serum hs-CRP level and prevalence of metabolic syndrome: Based on the 2015 Korean national health and nutrition examination survey. J Korean Diet Assoc. 2019;25(2):83-104.
    https://doi.org/10.14373/JKDA.2019.25.2.83

23. Wang X, Bao W, Liu J, Ouyang YY, Wang D, Rong S, et al. Inflammatory markers and risk of type 2 diabetes: A systematic review and meta-analysis. Diabetes Care. 2013;36(1):166-175.
    https://doi.org/10.2337/dc12-0702

24. Elimam H, Abdulla AM and Taha IM. Inflammatory markers and control of type 2 diabetes mellitus. Diabetes Metab Syndr. 2019;13(1):800-804.
    https://doi.org/10.1016/j.dsx.2018.11.061

25. Badimon L, Peña E, Arderiu G, Padró T, Slevin M, Vilahur G, et al. C-reactive protein in atherothrombosis and angiogenesis. Front Immunol. 2018;9:430.
    https://doi.org/10.3389/fimmu.2018.00430

26. Ridker PM. Clinical application of C-reactive protein for cardiovascular disease detection and prevention. Circulation. 2003;107(3):363-369.

https://doi.org/10.1161/01.CIR.0000053730.47739.3C

27. Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO 3rd, Criqui M, et al. Markers of inflammation and cardiovascular disease: Application to clinical and public health practice: A statement for healthcare professionals from the centers for disease control and prevention and the American heart association. Circulation. 2003;107(3):499-511.

https://doi.org/10.1161/01.CIR.0000052939.59093.45

28. Gelaye B, Revilla L, Lopez T, Suarez L, Sanchez SE, Hevner K, et al. Association between insulin resistance and c-reactive protein among Peruvian adults. Diabetol Metab Syndr. 2010;2(1):30.

https://doi.org/10.1186/1758-5996-2-30

29. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: Elaboration and explanation. BMJ. 2015;349:g76477.

https://doi.org/10.1136/bmj.g7647

30. Kamath D, Xavier D, Sigamani A and Pais P. High sensitivity C-reactive protein (hsCRP) and cardiovascular disease: An Indian perspective. Indian J Med Res. 2015;142(3):261-268.

https://doi.org/10.4103/0971-5916.166582

31. Mohan V, Unnikrishnan R, Shobana S, Malavika M, Anjana RM and Sudha V. Are excess carbohydrates the main link to diabetes and its complications in Asians? Indian J Med Res. 2018;148(5):531-538.

https://doi.org/10.4103/ijmr.IJMR_1698_18

32. Khare P, Talwar A, Chandran D, Guleria R, Jaryal AK, Kumar G, et al. Impaired systemic vascular reactivity and raised high-sensitivity C reactive protein levels in chronic obstructive pulmonary disease. Indian J Med Res. 2016;143(2):205-212.

https://doi.org/10.4103/0971-5916.180209

33. Indumathy J, Pal GK, Pal P, Ananthanarayanan PH, Parija SC, Balachander J, et al. Contribution of insulin resistance to decreased baroreceptor sensitivity and cardiometabolic risks in pre-obesity and obesity. Indian J Med Res. 2018;148(2):151-158.

https://doi.org/10.4103/ijmr.IJMR_1751_16

34. Enas EA, Kuruvila A, Khanna P, Pitchumoni CS and Mohan V. Benefits and risks of statin therapy for primary prevention of cardiovascular disease in Asian Indians-a population with the highest risk of premature coronary artery disease and diabetes. Indian J Med Res. 2013;138(4):461-491.

Authors Contributions:
BU- Carried out the experiment and collected the data and analyzed the data; **MLS-** Conceived and presented the idea, developed the theory and computations verified the analytical methods, and encouraged and supervised the findings of this work, and guided the entire work; **KLB-** Drafted the manuscript and aided in designing and writing the manuscript.

Work attributed to:
Sikkim Manipal Institute of Medical Sciences, Gangtok, Sikkim, India.

Orcid ID:
Dr. Benoy Upreti- ⓘ https://orcid.org/0009-0000-5528-1565
Dr. Mingma Lhamu Sherpa- ⓘ https://orcid.org/0000-0002-5905-6127
Dr. Karma Lakhi Bhutia- ⓘ https://orcid.org/0000-0003-1069-8775