Diabetes Mellitus as the Main Factor of Restenosis: Literature Review

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ABSTRACT

Introduction: Patients who have had cardiac stents have the risk of experiencing restenosis. The percentage of patients experiencing restenosis in RSUD Dr. Soetomo Surabaya in 2017 reached 43.75%. Not yet known the main factors causing restenosis affect the increase in mortality due to restenosis. Several studies suggest that diabetes mellitus is the factor that most consistently increases the risk of restenosis. This requires further research with the literature review method to analyze the continuity of the journals found.

Methods: Search for journals based on PRISMA, namely by the process of identification, screening, eligibility, and included. Sources of indexed journal searches are Scopus, Ebscohost using the CINAHL and ProQuest databases. The keywords used in general journal searches are "restenosis OR in-stent restenosis AND factors OR predictors AND diabetes mellitus". Journals are identified based on their focus and appropriate research results. Then the journal screening is carried out by analyzing the design, samples, variables, instruments, methods of analysis and research results. Furthermore, journals are assessed for their eligibility using The Joanna Briggs Institute (JBI) Critical Appraisal.

Results: The total number of journals that are suitable and subsequently reviewed in this study is 15 journals. Six journals stated DM as a restenosis factor, two journals stated BMI as the main factor, four journals mentioned other factors and two journals denied DM was a predictor of restenosis.

Conclusion: The results of a review of 15 journals found that diabetes mellitus was a factor that appeared consistently and had a role in the incidence of restenosis from lifestyle factors or disease history. It is based on the number of significant journals, the power of explanation and the novelty of the research.

1. INTRODUCTION

Patients who have had a heart stent inserted are at risk of experiencing restenosis. Restenosis is defined as narrowing of the vessel lumen to> 50% occlusion. Restenosis occurs on average 3-6 months after PCI. Several studies suggest that diabetes mellitus is the factor that most consistently increases the risk of restenosis(Buccheri et al., 2016). The percentage of patients experiencing restenosis reached 33 (Patrick W. Serruys, MD; John D. Rutherford, 2016). Whereas in Indonesia, especially at the Dr. Soetomo Surabaya Hospital in 2017, the results obtained from 32 patients after the installation of stents who were treated in April, 43.75% of patients experienced restenosis (Agustin, 2017).

Diabetes mellitus has a major role in determining and growing the restenosis process. This is due to the prothrombotic environment of the coronary vessels, including increased blood viscosity and decreased biological activity of antithrombin II,

fibrinogen and factor VII as well as increased platelet aggregation which can play a role in restenosis. Additionally, the effects of stimulatory growth factors such as insulin-like growth factors on VSMCs can lead to a greater degree of neointimal hiperplasia (Buccheri et al., 2016). Research on the factors that cause restenosis is widely found, where diabetes mellitus is one of the factors. However, there are no specific studies regarding diabetes mellitus as a major factor in restenosis. Writing this literature review aims to analyze the continuity of these journals so that it can be considered that diabetes mellitus is the main factor for restenosis.

2. METHOD

The search for English journals was carried out on three indexed journal search sources, namely Scopus, Ebscohost using the CINAHL and ProQuest databases published in the last five years (2015-2020). The keywords used in the journal search were "restenosis OR in-stent restenosis AND factors OR predictors AND diabetes mellitus". The method of searching and selecting journals includes identification, screening, eligibility, and included.

A number of journals that match the keywords are specified in the publication of the last five years (2015-2020), open access, in English, full text, diabetes mellitus subject area. There were 106 journals from Scopus, 2 journals from Ebscohost and 85 journals from ProQuest that matched the criteria.

A number of 193 journals were then identified based on their research focus and research results that were in accordance with the topic. There were 178 journals that did not focus on restenosis and its factors and obtained irrelevant results.

The remaining 15 journals will then be screened based on their titles and abstracts. The screening in the Scopus journal is adjusted to the journal quartile Q1. Then all journals were screened by analyzing designs, samples, variables, instruments, methods of analysis and research results. The results of the screening conducted, obtained 15 journals according to the topic and research criteria.

After screening, 15 journals were assessed for their eligibility for review. The assessment uses The Joanna Briggs Institute (JBI) Critical Appraisal instrument. The values that appear vary widely from 72.7% to 100%. Where the value obtained, the 15 journals are worthy of review.

3. RESULT

The total number of journals that are suitable and subsequently reviewed in this study is 15 journals. The distribution of sources used is 8 Scopus journals, 2 CINAHL journals and 5 ProQuest journals. All journals were published in the last five years (2015-2020) and most published in 2017 in China.

Fifteen journals were reviewed according to the results found, six journals said that diabetes mellitus was a factor in restenosis.

Two journals reviewed stated that body mass index is the risk of restenosis. Body mass index is also known to be a risk factor for diabetes mellitus (Kammler et al., 2017).

Four other journals mention various other factors that influence the occurrence of restenosis. These factors include age, LDL, VEGF level, stent diameter, post PCI diameter, MLD post PCI, MSA, SER, number of stents, total stent length, history of cardiovascular disease and CVA prior to stent placement.

Two journals that strongly argue that DM is not a predictor of restenosis. DM is not considered a predictor of restenosis in the short or long term.

4. DISCUSSION

Diabetes mellitus (DM) is a condition in which metabolic disorders occur, which can be in the form of damage to the pancreas, resulting in insulin deficiency or insulin resistance in the body's cells so that the impact of both conditions is an increase in blood glucose. Patients with ScR had diabetes more frequently (44% vs 20%; $p < 0.001$)(Polimeni et al.,

2017). Clinical factors such as age and diabetes mellitus status have been confirmed to increase the risk of restenosis (Kang et al., 2015).

Diabetes mellitus is a prognostic risk factor after stenting because diabetes mellitus is predicted to be a higher risk for restenosis. Patients with diabetes mellitus have an increased production of Advanced Glycation End (AGE) which can increase reactive oxygen and accelerate arterial veins and atherosclerosis, and ultimately lead to restenosis. Thus diabetes mellitus is predicted to be higher in increasing the risk of restenosis (J. Zhao et al., 2020).

This is explained in the study (Konigstein et al., 2018)diabetes mellitus has consistently been a predictor of an increased risk of revasculation, myocardial infarction (MI), and death after PCI. Diabetes mellitus is a risk factor for revascularization at 1 year only in patients with complex lesions. At 1 year, significantly more TLF, MACEs, ST and TVR were found in insulin-treated patients. The tendency for the incidence of MI was more in patients with insulin. At 2 years it was stated that MACEs and TVF were still more prevalent in insulin-treated patients. The incidence of TLF is higher. The typical pattern of diabetic coronary artery disease is characterized by greater atherosclerotic and diffuse disease. Smaller vessel diameter and poor collateral formation when compared to non-DM. In particular, PCI in DM patients is associated with increased restenosis rate, revascularization, ST and mortality. The higher rates of revascularization and mortality after PCI in DM patients are due to stent failure, especially restenosis and disease progression. In DM patients, the main cause of restenosis is intimal hyperplasia accelerated by a lot of vascular inflammation, endothelial dysfunction and insulin growth factor in vascular smooth muscle and neointimal cells. The characteristic pattern of coronary artery disease in DM is characterized by the presence of long, diffuse lesions and favorable location of the lesions which contribute to a higher risk of restenosis after PCI. The

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This is reinforced by research (Paramasivam et al., 2020)Patients with diabetes mellitus are at higher risk for restenosis due to excessive neointima hyperplasia, hypercoagulability, increased inflammatory response, endothelial dysfunction and the presence of comorbidities. In BMS insertion, diabetes mellitus is an independent risk factor for

restenosis and MACEs after PCI. Worse clinical outcomes were reported in DM patients after PCI compared to non-DM patients, even at DES insertion. Patients with DM have a three times higher tendency of vascular disease prevalence.

Research (Wolny et al., 2019) confirmed where regarding the prevalence of insulin-dependent diabetes mellitus. Similarly, a report from the Swedish Coronary Angiography Angioplasty Registry (SCAAR) shows increased mortality in patients who used insulin consecutively over time even after the first year of PCI. Insulin use indicates a more severe DM status, including complicated lesions. Experimental data (Ritsinger et al., 2015) which shows that insulin can speed up the atherosclerotic process. Insulin alone may not be the cause of an increased thrombotic stent. The most common event after PCI in diabetes mellitus patients is hospitalization for heart failure. Patients with diabetes mellitus have an increased risk of restenosis and stent thrombosis, therefore they are also at risk for coronary and cardiovascular disease.

Regarding other treatments diabetes mellitus has a lower response to clopidogrel and has lower levels of circulating active metabolites. This suggests increased platelet reactivity and an increased risk of thrombotic events. A recent study explains that patients with coronary disease as well as DM sufferers are carriers of the CYP2C19 * 2 phenotype who require 2-4 times higher doses of clopidogrel to obtain platelet reactivity similar to patients treated with 75mg who do not have DM (Ruedlinger et al., 2017).

From another point of view that has similarities to DM as an independent factor for restenosis, observations were made (Rai et al., 2015). Regarding the FFR, it was suggested that the post-stent FFR could be used to predict restenosis. However, it was also stated that the FFR is not the right tool for DM patients. This is because the FFR is not significant because there are several confounders that affect the coronary artery flow rate such as diabetes mellitus or hypertension. On the other hand, the prevalence of hypertension and DM was found to be higher in patients with coronary stenosis, which serves as a confounding factor because it is associated with higher microvascular resistance and potentially a higher FFR value.

Previous research also states that diabetes mellitus has a major role in determining and growing the restenosis process. Prothrombotic from diabetic coronary vessels, including increased blood viscosity, decreased biological activity of antithrombin II, fibrinogen and factor VIII and increased platelet aggregation, can play a role in the occurrence of DM. In addition, the effects of a stimulatory growth factor such as insulin-like growth factor-1 on VSMCs can lead to a greater degree of neointimal hyperplasia. Atherectomy specimens of restenotic lesions in diabetic patients do not show an increase in smooth muscle proliferation, but rather a greater fibrotic response that can lead to narrowing of the blood vessels.(Buccheri et al., 2016).

There is uncertainty in a study that states diabetes mellitus is not a significant predictor of restenosis in the study. However, the CREST trial reported that DM was a predictor of restenosis after CAS(Daou et al., 2016).

This is explained in a study reporting the same thing that there is no significant difference between DM and non-DM patients in the outcome during 1 year of BRS installation. But after one year, DM became a predictor of cardiovascular disease mortality, revascularization and ScR. Post-procedure residual stenosis and procedural parameters were associated with a greater and significantly greater outcome in the DM group(Anadol et al., 2018).

However, there are different conclusions to the research (L. Zhao et al., 2017)The biological effects of DM can lead to plaque growth, vascular instability and a risk of thrombosis. However, when comparing the results after PCI with the second DES insertion

showed that DM was no longer correlated with restenosis. DM is not an independent risk factor for MACEs in patients receiving repeated DES implantations for DES-ISR. DM is no longer an independent factor after DES insertion for certain populations, such as patients with vein graft lesions, simple lesions (ACC / AHA type A / B1 lesions) and unprotected left main.

This is confirmed by research (Kammler et al., 2017) Classic risk factors for atherosclerosis such as DM, hypercholesterolemia, hypertension and smoking did not differ significantly in the restenosis and non-restenosis groups.

Research (Yin et al., 2017) also found no significant difference between the restenosis and non-restenosis groups with respect to baseline characteristics. These characteristics include age, gender, hypertension, diabetes mellitus, smoking habits and laboratory results, namely TC, TG, HDL, LDL. It was found only that hs-CRP levels were higher in the restenosis group compared to the non-restenosis group.

The same is the case with research results (Wan et al., 2016)diabetes mellitus is an unfavorable factor for restenosis. However, there was no significant difference between the restenosis group and the non-restenosis group on the DM factor.

Diabetes mellitusbe a factor that appears consistently and has a role in the incidence of restenosis. The occurrence of restenosis in diabetes mellitus is also influenced by insulin therapy and diabetes mellitus treatment that is carried out. However, diabetes mellitus as the main factor in restenosis was not found in all types of stents, because there are other factors that are more influencing the occurrence of restenosis. Comparing the strength of the explanation and the novelty of the research obtained, it is concluded that diabetes mellitus is a major factor in lifestyle or disease history that affects the occurrence of restenosis.

RESEARCH LIMITATION

There are few studies on the relationship between diabetes mellitus and restenosis without other weighting factors, so it is not in accordance with the study criteria. Many journals are found that cannot be obtained in full text and are not open access.

CONCLUSION

The results of a review of 15 journals found that diabetes mellitus was a factor that appeared consistently and had a role in the incidence of restenosis from lifestyle factors or disease history. It is based on the number of significant journals, the power of explanation and the novelty of the research.

REFERRENCE

Anadol, R., Schnitzler, K., Lorenz, L., et al. (2018). Three-years outcomes of diabetic patients treated with coronary bioresorbable scaffolds. BMC Cardiovascular Disorders, 18 (1), 1–10.https://doi.org/10.1186/s12872-018-0811-7

Buccheri, D., Piraino, D., Andolina, G., & Cortese, B. (2016). Understanding and managing in-stent restenosis: A review of clinical data, from pathogenesis to treatment. Journal of Thoracic Disease, 8 (10), E1150 – E1162.https://doi.org/10.21037/jtd.2016.10.93

Daou, B., Chalouhi, N., Starke, RM, et al. (2016). Predictors of restenosis after carotid artery stenting in 241 cases. Journal of Neuro Interventional Surgery, 8 (7), 677–679.https://doi.org/10.1136/neurintsurg-2015-011783

Kammler, J., Blessberger, H., Lambert, T., et al. (2017). In-stent restenosis after interventional treatment of carotid artery stenoses: a long-term follow-up of a single center cohort. Clinical Research in Cardiology, 106 (7), 493–500.https://doi.org/10.1007/s00392-017-1078-1

Kang, J., Cho, YS, Kim, SW, et al. (2015). Intravascular ultrasound and angiographic predictors of in-stent restenosis of chronic total occlusion lesions. PLoS ONE, 10 (10), 1–16.https://doi.org/10.1371/journal.pone.0140421

Konigstein, M., Ben-Yehuda, O., Smits, PC, et al. (2018). Outcomes Among Diabetic Patients Undergoing Percutaneous Coronary Intervention With Contemporary Drug-Eluting Stents: Analysis From the BIONICS Randomized Trial. JACC: Cardiovascular Interventions, 11 (24), 2467–2476.https://doi.org/10.1016/j.jcin.2018.09.033

Paramasivam, G., Devasia, T., Jayaram, A., UK, A. et al. (2020). In-stent restenosis of drug-eluting stents in patients with diabetes mellitus: clinical presentation, angiographic features, and outcomes. Anatolian Journal of Cardiology, 23 (1), 28–34.https://doi.org/10.14744/AnatolJCardiol.2019.72916

Patrick W. Serruys, MD; John D. Rutherford, MC (2016). The Birth, and Evolution, of Percutaneous Coronary Interventions. American Heart Association, PCI, 97–100.https://doi.org/10.1161/CIRCULATIONAHA.116.023681

Polimeni, A., Weissner, M., Schochlow, K., et al. (2017). Incidence, Clinical Presentation, and Predictors of Clinical Restenosis in Coronary Bioresorbable Scaffolds. JACC: Cardiovascular Interventions, 10 (18), 1819–1827.https://doi.org/10.1016/j.jcin.2017.07.034

Rai, A., Bahremand, M., Saidi, MR, et al. (2015). The Value of Pre- and Post-Stenting Fractional Flow Reserve for Predicting Mid-Term Stent Restenosis Following Percutaneous Coronary Intervention (PCI). Global Journal of Health Science, 8 (7), 240–244.https://doi.org/10.5539/gjhs.v8n7p240

Ritsinger, V., Saleh, N., Lagerqvist, B., & Norhammar, A. (2015). High event rate after a first percutaneous coronary intervention in patients with diabetes mellitus. Circulation: Cardiovascular Interventions, 8 (6), 1–11.https://doi.org/10.1161/CIRCINTERVENTIONS.114.002328

Ruedlinger, J., Prado, Y., Zambrano, T., et al. (2017). CYP2C19∗2 Polymorphism in Chilean Patients with Stent Restenosis Development and Controls. BioMed Research International, 1–6.https://doi.org/https://doi.org/10.1155/2017/578371

Wan, YL, Tsay, PK, Chen, CC, et al. (2016). Coronary in-stent restenosis: predisposing clinical and stent-related factors, diagnostic performance and analysis of inaccuracies in 320-row computed tomography angiography. International Journal of Cardiovascular Imaging, 32, 105–115.https://doi.org/10.1007/s10554-016-0872-6

Wolny, R., Mintz, GS, Matsumura, M., et al. (2019). Intravascular Ultrasound Assessment of In-Stent Restenosis in Saphenous Vein Grafts. American Journal of Cardiology, 123 (7), 1052–1059.https://doi.org/10.1016/j.amjcard.2018.12.030

Yin, J., Shen, L., Ji, M., et al. (2017). Inverse Relationship between Serum VEGF Levels and Late In-Stent Restenosis of Drug-Eluting Stents. BioMed Research International, 2017.https://doi.org/10.1155/2017/8730271

Zhao, J., Wang, X., Wang, H., Zhao, Y., & Fu, X. (2020). Occurrence and predictive factors of restenosis in coronary heart disease patients underwent sirolimus-eluting stent implantation. Irish Journal of Medical Science, 189 (3), 907–915.https://doi.org/10.1007/s11845-020-02176-9

Zhao, L., Zhu, W., Zhang, X., He, D., & Guo, C. (2017). Effect of diabetes mellitus on long-term outcomes after repeat drug-eluting stent implantation for in-stent restenosis. BMC Cardiovascular Disorders, 17 (1), 1–7.https://doi.org/10.1186/s12872-016-0445-6