Effect of fibroblast growth factor 21 (FGF21) and Proprotein convertase subtilisin/kexin9 (PCSK9) in Patients with Myocardial Infarction

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Abstract

The study included measurement of the biomarkers FGF-21 and pcsk9 in patients with myocardial infarction (MI) compared with healthy subjects and finding a correlation between biomarkers with the gender (25 females and 25 males) as well as type ST-elevation of myocardial infarction (MI). Blood samples were collected from patients with of the injured and admitted to the intensive care cardiac unit (CCU) in Al-Sadder Teaching Hospital in Al-Najaf province/ Iraq during the period from July to September, 2022. they are met (25) of healthy subjects. The result of this study revealed there was exhibit significant increase ($p<0.05$) in serum levels of FGF-21 in the patient (post-catheterization) MI group compared with in control group (476.8±50.01 &±41.1 pg/ml respectively) , but PCSK9 showed a significant decrease ($p<0.05$) in the patient (pre catheterization) MI group compared with control (9.805±2.11&17.66 ±2.56 pg/ml respectively). There were also changes on the type of gender and little in the level of MI-STE in the concentration level of both markers, which led to the conclusion of the research that the markers FGF-21 and PCSK9 are considered important indicators of the response of MI patients to catheterization or not.

Keywords: Myocardial infarction, Catheterization, ECG, FGF-21, PCSK9.

1. Introduction

Myocardial infarction (MI), which is the primary cause of the high prevalence of ischemic heart disease, is also the primary cause of cardiovascular illnesses, which are the leading causes of human death (Virani et al., 2020). MI is described as the sudden ischemic death of cardiac tissue, which is myocardial necrosis brought on by severe and prolonged coronary artery ischemia and hypoxia (Yang et al., 2022). About half of all fatalities globally are caused by cardiovascular disorders, which account for more than four million deaths annually in just Europe (Townsend et al., 2015). Acute myocardial infarction (AMI), which accounts for the majority of mortality attributable to coronary artery disease, is the primary cause of death among individuals (Mendis et al., 2011). AMI incidence has increased steadily and quickly over the past few decades, with annual growth rates of over 3.5%, as a result of changes in human behavior and lifestyle, especially in developing nations (Benjamin et al., 2017). Every year, AMI is identified in about 10% of patients who come to emergency rooms with chest pain. (Haasenritter et al., 2012). The development of methods that would enable early detection and elimination of AMI attracted a lot of attention. The former would allow for quick, frequently life-saving interventions; the latter, a quick, secure patient discharge that would significantly lower healthcare costs. Acute chest pain in the presence of common ECG changes remains to be the main determinant of AMI diagnosis. However, only about 90% of patients who present with chest pain actually have AMI, and the ECG changes that indicate AMI have poor sensitivity and specificity (Haasenritter et al., 2012; Wang et al., 2018). Additionally, a small but not insignificant percentage of patients do not display overt symptoms and/or ECG alterations. The need for additional diagnostic criteria has been highlighted by this situation, and cardiac indicators have come to light as the most logical solution. Serial, daily cardiac biomarker measurement was initially only used as a method to retroactively corroborate the diagnosis of AMI. Since then, their significance has grown, and cardiac biomarker changes are now considered important diagnostic factors for AMI (Ibanez et al., 2018). Recent cardiovascular study has become more and more interested in fibroblast growth factor 21, another liver-secreted cytokine with anti-inflammatory properties. Previous research has revealed that FGF21 controls glycolipid metabolism and has anti-oxidative stress and anti-inflammatory effects (Fisher & Maratos-Flier, 2016; Luo et al., 2017). Previous research has revealed that the etiology of AMI is significantly influenced by inflammation, oxidative stress, and abnormalities in glycolipid metabolism (Tao et al., 2015; Neri et al., 2017; Zhang et al., 2018). As a result, we assume that FGF21 and the prognosis of AMI are linked. The ninth member of the proprotein convertase family, proprotein convertase subtilisin/kexin9 (PCSK9), is specifically designed to identify and degrade the

LDL receptor (LDLR) (Artenstein & Opal, 2011). The liver produced most of the circulating PCSK9 in peripheral blood (Zaid et al., 2008). The LDLR cannot be recycled to the cell membrane because the PCSK9-LDLR complex transports it to the lysosome for destruction (Xiao et al., 2019). In addition, PCSK9 has been found in a number of body organs, including the lung (Fagerberg et al., 2014), brain, and heart(Ding et al., 2018). Recent research has revealed that PCSK9 inhibitors are linked to early plaque formation, late plaque rupture, thrombosis, and angiogenesis in addition to their ability to decrease LDL (Norata et al., 2016). Independent of the low-density lipoprotein receptor, Sun et al. found that PCSK9 interacts with apolipoprotein B and inhibits its intracellular degradation (Sun et al., 2012). A clinical study revealed that PCSK9 levels correlate with a higher likelihood of future cardiovascular events regardless of LDL plasma levels (Leanderet al., 2016). In individuals with stable coronary artery disease, the clinical analysis revealed a correlation between PCSK9 levels and white blood cell count (Li et al., 2014), and PCSK9 had an impact on rheumatoid arthritis and sepsis (Komatsu & Takayanagi , 2012 ; Krabben et al., 2015). Therefore, the current research predicts that FGF21 and PCSK9 are associated with the diagnosis of AMI and the effect of catheterization on them.

2. Materials and Methods

The patients were diagnosed by physician basing on history, typical chest pain clinical presentation, positive electrocardiogram change (ECG), angiography and positive cardiac markers estimation., whereas all control had no history of chest pain, no history of admission to the CCU and normal resting ECG, the control were collected from out patients clinic. Fifty persons were divided into two study groups: myocardial infarction (MI) patients before and after catheterization included 25 subjects, and the control group was composed of 25 healthy men and women in order to compare. The blood samples were taken between July and September 2022 from the Coronary Care Unit (CCU) at Al-Sadder Teaching Hospital in the Iraqi region of Al-Najaf. Patients and the control group varied in age from 35 to 80. After centrifuging the serum at 3000 rpm for 10 minutes, it was suctioned, split into aliquots, and stored in Eppendorf tubes at -40 °C until used. Specific kits for measuring human FGF-21 and PCSK9 concentrations in serum were supplied by Beijing Solarbio Science & Technology Co., Ltd. A Catalog No: SEKH-0176. Statistical analysis was calculated by using the GraphPad Prism program (version 5).The comparison between the two groups was analyzed by t-test (Mean & SE) when the P-value < 0.05 was statistically significant (Mohy et al., 2022; Alabidi et al., 2023).

3. Results and discussion

3.1 Measurement serum level of FGF-21 in myocardial infarction patients

The result in figure 1 exhibit significant increase ($p<0.05$) in serum levels of FGF-21 in patient (post) MI group compared with in control group and between (pre.) and (post)patient MI group while there is non- significant difference ($p>0.05$) in serum levels of FGF-21 in patient (pre) MI group compared with in control. The phosphatidylinositol 3-kinase/Akt (PI3K/Akt), ERK1/2 (extracellular signal-regulated kinase), and AMPK (AMP-activated protein kinase) pathways may all be triggered in heart tissue by the FGF21 signaling pathway. (Patel et al.,2014). Furthermore, despite the fact that FGF21 is an endocrine FGF, the heart also seems to be a focus of locally produced FGF21. According to a prior research, after myocardial injury, adipose tissue releases FGF21, which acts via the FGFR1/b-Klotho-PI3K-Akt1-BAD signaling network to protect the heart. (Liu SQ et al.,2012) This supports a prior study's conclusion that the level of FGF21 can predict morbidity and mortality in coronary heart disease (Lenart et al.,2013). An earlier investigation revealed that cardiomyocytes made and secreted FGF21 (Planavila et al.,2013) . Cardiac FGF21 was secreted in reaction to cardiac ischemic stress, and it prevented isoproterenol-induced cardiac hypertrophic injury. Also The result in figures (2) exhibit significant increase ($p<0.05$) in serum levels of GF-21 in (pre) and (post) men patient MI group compared with in control, while there is non-significant difference ($p>0.05$) in serum levels of GF-21 in (pre) and (post) men patient MI group compared between of them. The result in figures (3) exhibit non-significant difference ($p>0.05$) in serum levels of GF-21 in (pre) and (post)women patient MI group compared with in control group. The difference in risk factors between men and women in this research may be explained by the role that sex hormones play in atherosclerosis. One research found a link between serum FGF21 and estradiol that was detrimental, protecting premenopausal women from CVD (Zhang et al.,2015). The various mechanism(s) underpinning the connection between sex hormones and FGF21 in relation to CVD are still unknown (Chow et al., 2013). The result in figure (4) exhibit non-significant elevation ($p>0.05$) in serum levels of GF-21 in (pre) and (post) patient MI-STE segment group compared with in control group. This finding conflicts with that of Sunaga et al., who discovered that patients with AMI following PCI had substantially higher serum FGF21 levels (Sunaga et al., 2019). Another investigation revealed a link between FGF21 and AMI. (Zhang et al., 2015). Chen et al. discovered that FGF21 was associated with AMI, which is in line with our findings (Chen, Lu & Zheng, 2018).

3.2 Measurement of serum level of PCSK9 in myocardial infarction patients

The result in figure (5) exhibit significant decrease ($p<0.05$) in serum levels of PCSK9 in patient (pre) MI group compared with in control while, but there is non-significant difference ($p>0.05$) in serum levels of PCSK9 in patient (post) MI group compared with in patient (pre.) MI group and control group. After acute MI, rodents' PCSK9 levels were found to be increased (Zhang et al., 2014), which is also supported in people because patients with acute MI also have elevated serum levels of PCSK9. This could be explained by the fact that acute MI increases PCSK9 expression by increasing the transcript of SREBP-2, hepatocyte nuclear factor 1 (HNF1), and NLRP3 (Andreadou et al., 2020). Furthermore, MI causes the cardiomyocytes to become hypoxic, and it has been shown that hypoxia stimulates PCSK9 mRNA in cultured cardiomyocytes. Even in healthy cardiomyocytes, the PCSK9 produced by hypoxic cardiomyocytes causes injury. (Yang et al., 2020). Moreover, the elevated PCSK9 levels also stimulate the secretion of pro-inflammatory cytokines and activate NF-κB signalling in the recruited macrophages at the sites of injury (Yang et al., 2020). Additionally, Laugsand et al. showed that a correlation existed between elevated risk of MI and PCSK9 blood levels (Laugsand et al., 2016). Therefore, Zhang et al. showed that the acute stage of AMI in the rat model greatly increased the plasma concentration of PCSK9, which was supported by elevated levels of liver mRNA. (Zhang et al., 2014). Their findings are in line with genetic research that has indicated a link between a lower plasma level of PCSK9 and a lower risk of MI. (Benn et al., 2010; Kathiresan, 2008; Cohen et al., 2006). Recent research by Qi et al. indicated a connection between PCSK9 and increased platelet activation (Qi et al., 2021). The result in figure (6) non-significant difference ($p>0.05$) in serum levels of PCSK9 in (pre) and (post)men patient MI group compared with in control and compared between them, while, The result in figures (7) exhibit significant decrease ($p<0.05$) in serum levels of PCSK9 in (pre) and (post)women patient MI group compared with in control group, but there is non-significant difference ($p>0.05$) in serum levels of PCSK9 compared between (pre) and (post) women patient MI group. The study of PCSK9 is of great practical interest. In one study, the authors investigated the PCSK9 levels in men (44-73 years) in different population subgroups, its relationship with cardiovascular risk factors and long-term 7-year unfavorable prognosis, where the mean level of PCSK9 was significantly lower (Ragino et al., 2017). In another population-based study of men aged 25-45, the mean PCSK9 level there were also higher variability (Benimetskaya et al., 2019), this agree with our study. Several researchers have identified differences in PCSK9 levels depending on gender and BMI. So, in the Dallas Heart Study, the PCSK9 level was higher in women than in men [(Benimetskaya et al., 2019; Lakoski et al., 2009), which was dis

agreement with our study. The result in figure (8) exhibit significant decrease ($p<0.05$) in serum levels of PCSK9 in (pre) patient of MI-STE(V1-V6) and MI-STE(II,III,avF) group compared with in control group. while the result showed non- significant difference ($p>0.05$) in serum levels of PCSK9 in (pre) patient of MI-STE(V1-V4), (V1-V5) compared with in control group, also there is non- significant difference ($p>0.05$) in serum levels of PCSK9 in (post) patient of MI-STE(V1-V4), (V1-V5), (V1-V6), (II, III, avf) compared with in control group. There is controversy about the effect of the level of PCSK9 in the blood, Laugasnd et al 2016 stated that the levels of PCSK9 in the blood do not indicate any effect when available with measurements of the level of lipids, while Uzui et al, 2019 warn that the indicator of the level of PCSK9 as a treatment in the acute phase after AMI has beneficial effects It lowers levels with the LDL-C index and becomes a useful treatment in reducing LV and thus improving LV function. The independent PCSK9 level predicted all cardiovascular events and mortality for all causes of black African dialysis patients (Kajiuglu etal, 2022), while myocardial infarction in patients with high blood pressure, the PCSK9 level is a good indicator for the most effective PPCI infarction treatment strategy. For the treatment of ST-segment elevation myocardial infarction (STEMI) (Xia etal, 2022). The current study concluded that FGF21 and PCSK9 markers could be important indicators in the treatment of myocardial infarction patients after catheterization.

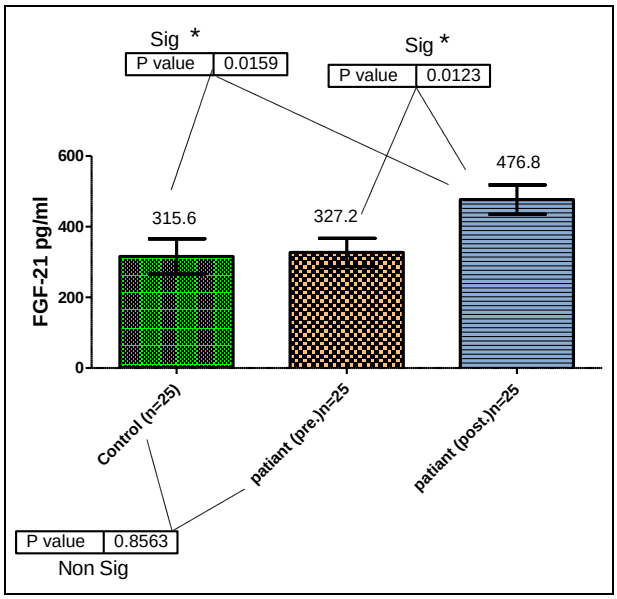

Figure 1: Comparison of serum GF-21 level between (pre.), (post.) myocardial infarction patient and control group. (*): Statistically significant differences ($p<0.05$).

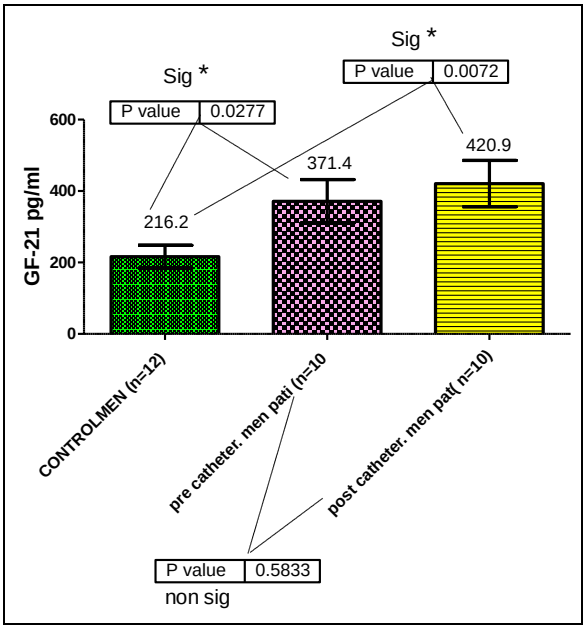

Figure 2: Comparison of serum GF-21 level between (pre.), (post.) men of myocardial infarction patient and control group. (*): Statistically significant differences ($p<0.05$).

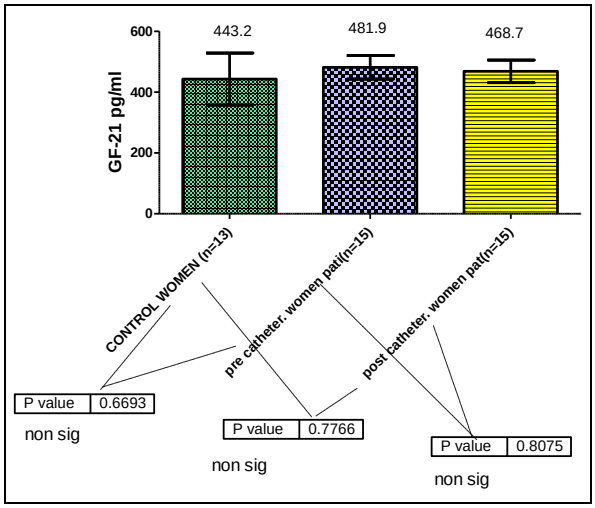

Figure 3: Comparison of serum GF-21 level between (pre.), (post.) women of myocardial infarction patient and control group. (*): Statistically significant differences ($p<0.05$).

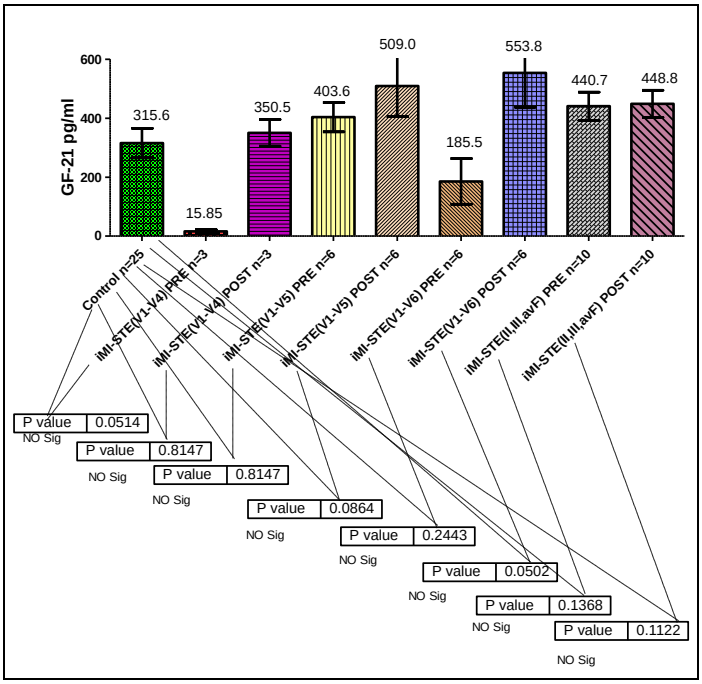

Figure 4: Comparison of serum GF-21 level (pre.), (post.) between types ST elevation of myocardial infarction patient group. (*): Statistically significant differences ($p<0.05$).

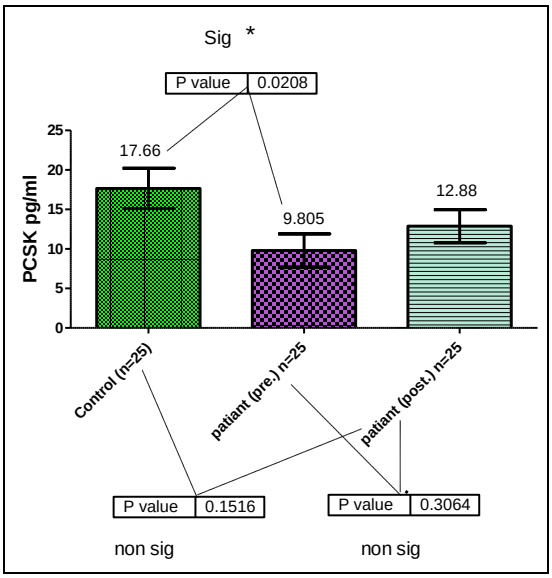

Figure 5: Comparison of serum PCSK9 level between (pre.), (post.) myocardial infarction patient and control group. (*): Statistically significant differences ($p<0.05$).

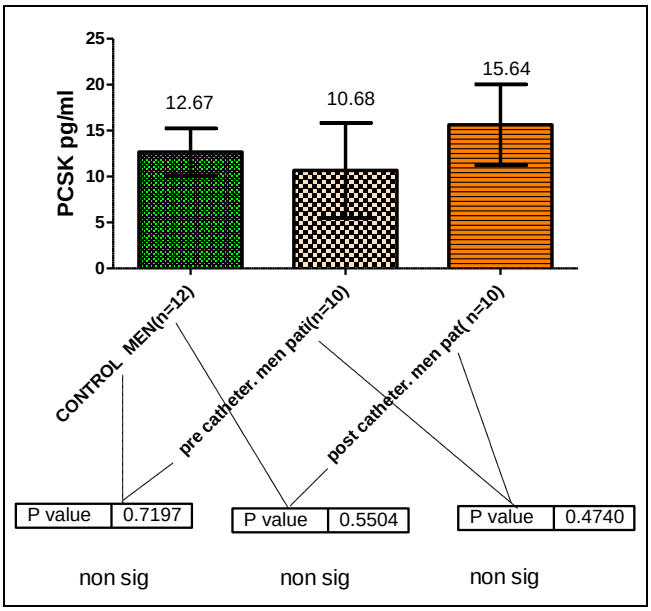

Figure 6: Comparison of serum PCSK9 level between (pre.), (post.) men of myocardial infarction patient and control group. (*): Statistically significant differences ($p<0.05$).

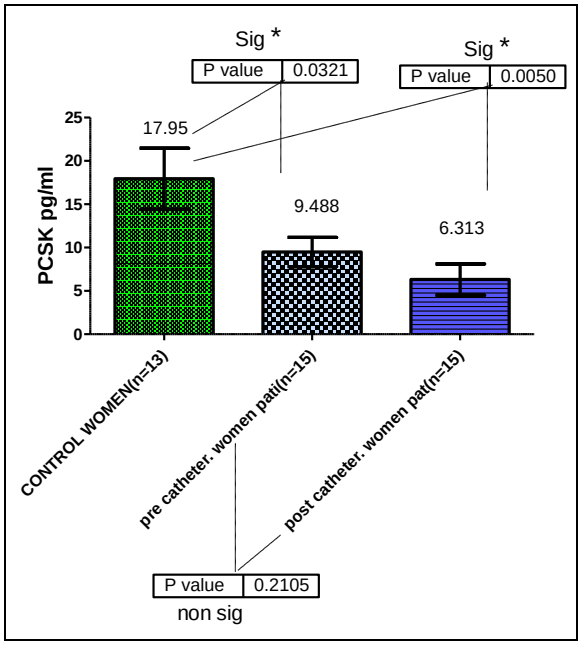

Figure 7: Comparison of serum PCSK9 level between (pre.), (post.) women of myocardial infarction patient and control group. (*): Statistically significant differences ($p<0.05$).

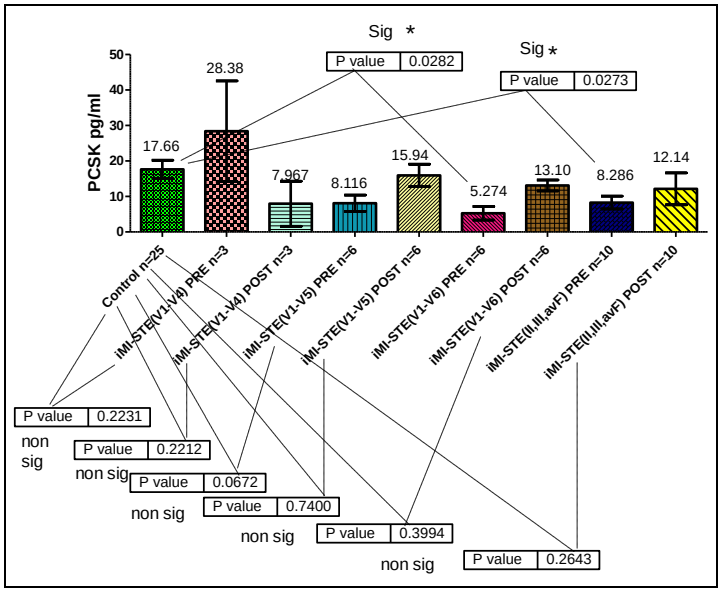

Figure 8: Comparison of serum PCSK9 level (pre.), (post.) between types ST elevation of myocardial infarction patient group. (*): Statistically significant differences ($p<0.05$).

4. Conclusions

The FGF-21 and PCSK9 Markers are considered important indicators of the response of MI patients to catheterization.

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