PERANAN LALUAN ISYARAT α1NACHR-ERK DALAM PEMBENTUKAN MATRIKS METALLOPROTEINASE DALAM KALANGAN PEROKOK LELAKI DENGAN SINDROM KORONARI AKUT

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PERANAN LALUAN ISYARAT α1NACHR-ERK DALAM PEMBENTUKAN MATRIKS METALLOPROTEINASE DALAM KALANGAN PEROKOK LELAKI DENGAN SINDROM KORONARI AKUT

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PENGAKUAN

Saya akui karya ini adalah hasil kerja saya sendiri kecuali nukilan dan ringkasan yang tiap-tiap satunya telah saya jelaskan sumbernya.

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ABSTRAK

Sindrom koronari akut (ACS) merupakan manifestasi klinikal penyakit arteri koronari (CAD) yang kritikal berpunca daripada kepecahan plak aterosklerotik tidak stabil yang menyebabkan arteri koronari menjadi sempit dan mengurangkan bekalan darah ke miokardium. Merokok meningkatkan risiko ACS melalui pengaktifan enzim matriks metalloproteinase (MMP) yang mendegradasi lapisan fibrosa plak, manakala perencat tisu metalloproteinase (TIMP) berperanan menentang aktiviti tersebut. Walau bagaimanapun, mekanisme molekul yang mengaitkan tabiat merokok dengan peningkatan MMP dalam ACS masih belum difahami sepenuhnya. Kajian ini bertujuan mengkaji peranan laluan isyarat α1nAChR–ERK terhadap pembentukan MMP dalam tisu plak aterosklerotik dan sel mononuklear darah periferi (PBMC) pesakit CAD. Sebanyak 41 tisu plak aterosklerotik diperoleh daripada subjek yang meninggal akibat CAD (26 perokok, 15 bukan perokok), manakala 180 subjek klinikal direkrut [n = 30 setiap kumpulan: ACS, sindrom koronari kronik (CCS) dan Kawalan; perokok dan bukan perokok]. Ekspresi gen α1nAChR, ERK 1/2 dan c-FOS dianalisis menggunakan RT-qPCR, manakala paras protein MMP-2, MMP-9 dan TIMP 3 ditentukan melalui ELISA. Skor Gensini diperoleh daripada penemuan angiogram, manakala parameter fungsi jantung [pecahan ejeksi ventrikel kiri (LVEF), halaju E, nisbah E/A, purata nisbah E/e', dan masa nyahpecutan gelombang E (EDT)] ditentukan melalui ekokardiografi. Keputusan menunjukkan ekspresi ERK 1/2 dan c-FOS adalah lebih tinggi (1.671 kali ganda dan 1.327 kali ganda) dalam tisu plak aterosklerotik perokok berbanding bukan perokok ($p<0.05$), manakala α1nAChR tidak berubah. Dalam PBMC, α1nAChR adalah lebih tinggi (1.383 kali ganda, $p<0.05$) dalam CCS perokok, manakala ERK 1/2 adalah lebih tinggi (1.355 kali ganda, $p<0.001$) dalam ACS perokok berbanding CCS bukan perokok. Dalam kalangan perokok dan bukan perokok, MMP-9 dalam ACS dan CCS adalah lebih tinggi secara signifikan berbanding Kawalan ($p<0.001$). Dalam CCS, MMP-9 dalam kalangan perokok adalah lebih tinggi berbanding bukan perokok (364.75 ± 1.2 vs 197.24 ± 1.2 ng/mL, $p=0.036$). Manakala, TIMP 3 adalah lebih tinggi secara signifikan dalam kumpulan CCS perokok berbanding Kawalan perokok (26.98 ± 1.1 vs 16.94 ± 1.1, $p<0.001$). Seterusnya, MMP-9 berkorelasi positif dengan skor Gensini ($r=0.556$, $p<0.001$) dan negatif dengan LVEF ($r=-0.267$, $p<0.001$) dalam kalangan perokok. Kesimpulannya, merokok mengaktifkan laluan isyarat α1nAChR–ERK melalui peningkatan ERK 1/2 dalam tisu plak aterosklerotik serta peningkatan α1nAChR dan ERK 1/2 dalam PBMC, mencerminkan tindak balas tempatan dan sistemik terhadap pendedahan nikotin. Pengaktifan laluan ini meningkatkan ekspresi MMP-9, seterusnya menyumbang kepada ketidakstabilan plak, peningkatan risiko perkembangan ACS, serta disfungsi jantung dalam pesakit CAD.

THE ROLE OF α1NACHR-ERK 1/2 SIGNALING PATHWAY IN MATRIX METALLOPROTEINASE FORMATION AMONG MALE SMOKERS WITH ACUTE CORONARY SYNDROME

ABSTRACT

Acute coronary syndrome (ACS) is a critical clinical manifestation of coronary artery disease (CAD) resulting from the rupture of unstable atherosclerotic plaques that causes coronary arteries to narrow and reduced blood supply to the myocardium. Smoking increases the risk of ACS by activating matrix metalloproteinases (MMP), which degrade the fibrous cap of plaques, while tissue inhibitors of metalloproteinases (TIMP) counteract this activity. However, the molecular mechanisms linking smoking and increased MMP activity in ACS remain unclear. This study aimed to investigate the role of the α1nAChR–ERK signaling pathway in MMP formation within atherosclerotic plaque tissues and peripheral blood mononuclear cells (PBMCs) of CAD patients. Forty-one atherosclerotic plaque samples were obtained from subjects who died due to CAD (26 smokers, 15 non-smokers), while 180 clinical subjects were recruited [n = 30 per group: ACS, chronic coronary syndrome (CCS), and controls; smokers and non-smokers]. Gene expression of α1nAChR, ERK 1/2, and c-FOS was analyzed using RT-qPCR, while protein levels of MMP-2, MMP-9, and TIMP 3 were determined by ELISA. The Gensini score was derived from angiogram findings, whereas cardiac function parameters [left ventricular ejection fraction (LVEF), E velocity, E/A ratio, average E/e' ratio, and E-wave deceleration time (EDT)] were determined by echocardiography. Results showed higher expression of ERK 1/2 and c-FOS (1.671-fold and 1.327-fold) in atherosclerotic plaque tissues of smokers compared to non-smokers ($p<0.05$), while α1nAChR remained unchanged. In PBMCs, α1nAChR expression was higher (1.383-fold, $p<0.005$) in CCS smokers, and ERK 1/2 expression was higher (1.355-fold, $p<0.001$) in ACS smokers compared to CCS non-smokers. Among smokers and non-smokers, MMP-9 in ACS and CCS were significantly higher compared to Controls ($p<0.001$). In the CCS, MMP-9 was higher in smokers than in non-smokers (364.75±1.2 vs 197.24±1.2 ng/mL, $p=0.036$). Meanwhile, TIMP 3 were significantly higher in smokers with CCS compared to smoker Controls (26.98±1.1 vs 16.94±1.1, $p<0.001$). Furthermore, MMP-9 showed a positive correlation with Gensini score ($r=0.556$, $p<0.001$) and a negative correlation with LVEF ($r=-0.267$, $p<0.001$) among smokers. In conclusion, smoking activates the α1nAChR–ERK signaling pathway through increased ERK 1/2 expression in atherosclerotic plaque tissue, as well as upregulation of α1nAChR and ERK 1/2 in PBMCs, reflecting both local and systemic responses to nicotine exposure. This pathway activation enhances MMP-9 expression, contributing to plaque instability and increased risk of ACS progression, and cardiac dysfunction in CAD patients.

KANDUNGAN

SENARAI JADUAL

No. Jadual **Halaman**

SENARAI ILUSTRASI

SENARAI SINGKATAN

%	peratus
ΔΔCT	kitaran ambang
°C	darjah celcius
µL	mikro liter
α1nAChR	reseptor nikotinik asetilkolina alfa-1
α1-AAV	vektor virus berkaitan adenon alfa-1
α3β1-integrin	alfa-3 beta-1 integrin
ACS	sindrom koronari akut
ADAM	disintegrin dan metalloproteinase
ADAMTS	disintegrin dan metalloproteinase dengan motif trombospondin
AGTRI/2	reseptor angiotensin II jenis 1
ATF	faktor transkripsi pengaktif
ANOVA	analisis varians
ANCOVA	analisis kovarians
AP-1	protein pengaktif-1
Apo E	apolipoprotein E
Av E/e'	purata nisbah halaju pengisian awal kepada halaju anulus mitral diastolik awal
BATF	protein mirip ATF yang mengandungi domain *zipper leucine*
BCA	asai asid bikinkoninik
CAD	penyakit arteri koronari
CCS	sindrom koronari kronik
CD63	sel kluster pembezaan 63
CeVD	penyakit serebrovaskular
c-FOS	protein selular FOS
c-JUN	protein selular JUN
CHD	penyakit jantung kongenital
cm	sentimeter
CT	nilai kitaran ambang

CVD	penyakit kardiovaskular
DALYS	*disability-adjusted life years*
DM	diabetes mellitus
DNA	asid deoksiribonukleik
dNTP	deoksinukleosida trifostat
E	halaju pengisian awal diastolik
E/A	nisbah halaju pengisian awal mitral kepada halaju pengisian atrial
ECG	elektrokardiogram
ECM	matriks ekstraselular
EDT	masa nyahpecutan gelombang E
EDTA	tiub mengandungi asid etilenediamintetraasetik
EFEMP1	protein matriks ekstraselular menyerupai fibulin dengan domain EGF1
ELISA	asai imunosorben pautan enzim
ERK 1/2	kinase terkawal isyarat ekstraselular 1 dan 2
ET-1	endotelin-1
g	gram
GENLIN	model linear umum dengan pautan log gamma
GLM	model linear umum
Hs-CRP	protein C-reaktif berkepekatan tinggi
HRP	*horseradish peroxidase*
Hz	hertz (unit frekuensi)
ICAM-1	molekul lekatan antara sel-1
IHD	penyakit jantung iskemik
IL-β	interleukin beta
JDP2	protein pengdimeran Jun 2
K^+	ion kalium
kDa	kilodalton (unit jisim molekul)
LA	atrium kiri
LAD	arteri menurun anterior kiri
LAP	tekanan atrium kiri
LCx	anteri sirkumfleks kiri

LBBB	sekatan berkas kiri
LDL-C	kolesterol lipoprotein berketumpatan rendah
LRP-1	protein berkaitan reseptor lipoprotein berketumpatan rendah 1
LV	ventrikel kiri
LVEF	pecahan ejeksi ventrikel kiri
LVDF	gangguan fungsi diastolik ventrikel kiri
LVFP	tekanan pengisian ventrikel kiri
MAPK	protein kinase diaktifkan mitogen
MI	infark miokardium
MINOCA	infark miokardium dengan arteri koronari tidak tersumbat
MMP-2	matriks metalloproteinase-2
MMP-9	matriks metalloproteinase-9
M-MuLV	virus Moloney *Murine Leukemia*
m/s	meter per saat
mg	miligram
mL	mililiter
MVD	penyakit pelbagai salur
NA^+	ion natrium
NFATc1	faktor nuklear sel T teraktif 1
nm	nanometer
NO	nikrik oksida
NCVD-ACS	pangkalan Data Penyakit Kardiovaskular Kebangsaan Malaysia-Sindrom Koronari Akut
NSTEMI	infark miokardium tanpa peningkatan segmen ST
O_2^-	superoksida
OD	ketumpatan optik
$ONOO^-$	peroksinitrit
Oligo d(T)	oligo deoksitiamina
OxLDL	lipoprotein berketumpatan rendah teroksida
PAD	penyakit arteri periferal
PBMC	sel mononuklear darah periferi
PBS	larutan penimbal fosfat
PCI	intervensi koronari perkutaneus

PDA	arteri menurun posterior
pH	unit keasidan/kealkalian larutan
p38MAPK	protein kinase diaktifkan mitogen p38
P13K/Akt	fosfoinositida 3-kinase/protein kinase B
PMI	infark miokardium periprosedure
RANK	reseptor pengaktif faktor nuklear-κB
RHD	penyakit jantung reumatik
RNA	asid ribonukleik
RT-qPCR	tindak balas berantai polimerase kuantitatif transkripsi sonsang
SST	tiub pemisah serun
STEMI	infark miokardium dengan peningkatan segmen ST
TCFA	*thin cap fibroatheroma*
TIA	serangan iskemia sementara
TIMP 3	perencat tisu metalloproteinase 3
TNFα	faktor nekrosis tumor-alfa
UA	angina tidak stabil
VCAM-1	molekul lekatan sel vaskular
VEGFR	faktor pertumbuhan vaskular endotelium
VSMC	sel otot licin vaskular

BAB I

PENGENALAN

1.1 PENDAHULUAN

Penyakit kardiovaskular (CVD) adalah penyumbang utama kepada kematian dan morbiditi global. Sebanyak 20.5 juta kematian yang merangkumi satu pertiga daripada semua kematian global pada tahun 2021 adalah disebabkan oleh CVD (Lindstrom et al. 2022). Dalam kalangan jenis-jenis penyakit CVD, penyakit jantung iskemik (IHD) adalah yang paling berleluasa (Roth et al. 2017). Di Malaysia, statistik oleh Jabatan Perangkaan Malaysia pada tahun 2023 menunjukkan IHD adalah penyebab utama kematian pada tahun 2022, iaitu sebanyak 20,322 kematian atau 16.1% telah direkodkan (Jabatan Perangkaan Malaysia 2023). Dianggarkan bahawa pada tahun 2050, IHD akan menjadi penyumbang terbesar kepada beban kematian CVD yang diselaraskan umur, iaitu 416 kematian bagi setiap 100,000 penduduk di negara asia tengah (Goh et al. 2024).

IHD atau turut dikenali sebagai penyakit arteri koronari (CAD) adalah penyakit kekurangan bekalan darah dan oksigen kepada sel otot jantung akibat pembentukan plak di dalam salur arteri koronari (Shahjehan et al. 2024). Proses patofisiologi utama yang membawa kepada CAD ialah aterosklerosis, iaitu penyakit radang arteri yang dikaitkan dengan pemendapan lipid dan perubahan metabolik akibat pelbagai faktor (Ambrose & Singh 2015; Falk et al. 2013; Hanson et al. 2013). Terdapat dua klasifikasi CAD iaitu sindrom koronari akut (ACS) dan sindrom koronari kronik (CCS). ACS adalah manifestasi klinikal CAD yang paling kritikal kerana pembentukan plak yang tidak stabil dan terjadinya kepecahan plak aterosklerotik. Kepecahan plak ini mengakibatkan pembentukan trombus yang akan menyekat atau mengurangkan aliran darah ke otot jantung secara mendadak (Kitulwatte & Pollanen 2015). ACS diklasifikasikan kepada tiga kategori utama, iaitu infark miokardium dengan peningkatan segmen ST (STEMI), infark miokardium tanpa peningkatan segmen ST (NSTEMI), dan angina tidak stabil (UA). Kesemua keadaan ini berpotensi menyebabkan komplikasi serius, termasuklah serangan jantung, kegagalan fungsi jantung, dan kematian mengejut sekiranya tidak dirawat dengan segera (Kementerian Kesihatan Malaysia 2011). Menurut laporan tahunan pendaftaran Pangkalan Data Penyakit Kardiovaskular Kebangsaan Malaysia-Sindrom Koronari Akut (NCVD-ACS), terdapat 15,162 pesakit ACS telah dimasukkan di hospital pada tahun 2020-2021. Daripada jumlah itu, 50.3% pesakit didiagnosis dengan STEMI, 30.4% adalah NSTEMI, dan 19.3% adalah UA. Kebanyakan pesakit adalah lelaki (79.4%) dan muda dengan purata umur semasa kemasukan adalah 58.5 tahun (Wan Ahmad 2024).

Terdapat beberapa faktor risiko yang menyumbang kepada perkembangan ACS termasuk hipertensi, hiperkolesterolemia, diabetes mellitus, obesiti, gaya hidup tidak sihat, dan sejarah keluarga penyakit jantung (American Heart Association 2024). Walau bagaimanapun, salah satu faktor risiko yang paling signifikan dan boleh diubah untuk ACS adalah merokok. Kajian menunjukkan bahawa perokok mempunyai risiko hampir dua kali ganda lebih tinggi untuk mengalami ACS berbanding bukan perokok (Banks et al. 2019). Risiko ini meningkat dengan bilangan rokok yang dihisap setiap hari dan berkurang dalam kalangan bekas perokok (Banks et al. 2019). Merokok menyumbang kepada perkembangan dan kemajuan aterosklerosis, melalui disfungsi endotelium, peningkatan tekanan oksidatif, dan keradangan arteri (Addissouky et al. 2024; Hahad et al. 2023). Merokok juga mengurangkan ketahanan plak aterosklerotik dengan merosakkan lapisan fibrosa, yang berfungsi sebagai pelindung matriks ekstraselular (ECM) di salur arteri koronari. Satu kajian sistematik oleh Aminuddin et al. (2023) mendapati bahawa merokok meningkatkan degradasi lapisan fibrosa tersebut dengan meningkatkan aktiviti enzim matriks metalloproteinase (MMP). MMP adalah satu keluarga enzim endopeptidase yang bergantung kepada zink dan menpunyai aktiviti proteolitik terhadap ECM (Hey & Linder 2024). Enzim-enzim ini akan merosakkan kolagen dan komponen struktur lain dalam ECM, seterusnya mengakibatkan penipisan dan kerosakan pada lapisan fibrosa itu. Perubahan patofisiologi ini mempercepatkan pembentukan plak aterosklerotik yang tidak stabil dan meningkatkan risiko plak untuk pecah, satu kejadian utama yang membawa kepada ACS (Naghavi et al. 2003; Teresa et al. 2023).

Terdapat beberapa jenis MMP yang berkait rapat dengan ketidakstabilan plak aterosklerotik, antaranya ialah MMP-2 dan MMP-9. MMP-2 atau juga dikenali enzim gelatinase A yang secara khususnya mengurai kolagen jenis IV, laminin dan elastin dalam ECM (Sanyal et al. 2022; Wolosowicz et al. 2024). Penguraian ini memberi kesan kepada pengubahsuaian vaskular dan angiogenesis (Salajeghah 2016). Aktiviti MMP-2 juga mengaktifkan MMP yang lain, termasuklah MMP-9, dan meningkatkan lagi kerosakan ECM serta ketidakstabilan plak. MMP-9 juga dikenali sebagai enzim gelatinase B, secara khususnya mengurai kolagen jenis I dan III iaitu kolagen penting untuk mengekalkan integriti struktur lapisan fibrosa yang melindungi plak aterosklerotik. MMP-9 dilepaskan oleh sel-sel makrofaj dan neutrofil ke lapisan serat plak dan meningkatkan keradangan dan pemecahan ECM (Newby 2016). Pemecahan ECM dalam lapisan fibrosa membawa kepada pendedahan teras lipid trombogenik dan pembentukan trombus, seterusnya, menyebabkan ACS. Kajian yang terdahulu mendapati bahawa kedua-dua MMP-2 dan MMP-9 meningkat dalam pesakit ACS dan dianggap sebagai penanda biologi ketidakstabilan dah kepecahan plak aterosklerotik (Ezhov et al. 2019; Funayama et al. 2021). Ini menunjukkan tahap MMP yang tinggi mencerminkan beban aterosklerosis yang lebih besar dan berpotensi untuk menilai keterukan CAD (Bräuninger et al. 2023; Marynenko et al. 2022). Skor Gensini, iaitu alat ukuran untuk menilai tahap keterukan penyakit CAD dengan mengkuantifikasi tahap dan lokasi stenosis arteri telah digunakan dalam kajian oleh Yu et al. (2012). Dalam kajian ini, mereka mendapati terdapat korelasi yang signifikan antara tahap MMP-2 dan MMP-9 yang meningkat dan skor Gensini yang lebih tinggi, mencadangkan bahawa peningkatan aktiviti MMP dikaitkan dengan kecederaan arteri koronari yang lebih teruk (Yu et al. 2012).

Selain itu, MMP juga dikaitkan dengan pengubahsuaian dan kejejasan fungsi ventrikel kiri (LV), iaitu tanda penting dalam pesakit ACS (Esmaeilzadeh et al. 2013). Kajian telah menunjukkan bahawa kepekatan MMP-9 yang lebih tinggi berkorelasi dengan peningkatan volum LV dan pengurangan pecahan ejeksi (EF), seperti yang diperhatikan melalui pengukuran ekokardiografi (Lahdentausa et al. 2018). Kajian oleh Durcharme et al. (2000) juga mendapati penghapusan gen MMP-9 yang disasarkan dapat dikaitkan dengan pengurangan kejadian LV pecah. Perkaitan ini menekankan potensi MMP-9 sebagai penanda biologi untuk meramalkan pengubahsuaian jantung dan membimbing strategi terapeutik dalam rawatan ACS.

Perencatan ekspresi dan aktiviti MMP boleh mengurangkan risiko keparahan aterosklerosis dan terjadinya ACS. Perencat tisu metalloproteinase (TIMP) adalah protein endogen yang berfungsi untuk menentang aktiviti penguraian oleh MMP. Protein ini memainkan peranan penting dalam mengekalkan keseimbangan antara sintesis dan degradasi ECM (Hey & Linder 2024). TIMP akan mengikat pada tapak aktif ECM dan menghalang aktiviti enzimatik MMP, seterusnya melindungi komponen ECM daripada degradasi berlebihan (Chintalgattu et al. 2018). Proses ini dapat mengurangkan kepecahan plak aterosklerotik dan menurunkan risiko ACS. Di antara empat keluarga TIMP yang lain, TIMP 3 adalah yang paling unik kerana ia mempunyai afiniti yang tinggi terhadap proteoglikan dalam ECM dan mempunyai julat substrat yang luas, termasuk semua MMP (Takawale et al. 2015). Kajian rawak mendelian (MR) oleh Chen et al. (2022) mendapati kandungan TIMP 3 yang tinggi dalam serum boleh mengurangkan risiko ACS dalam kalangan pesakit kardiovaskular, manakala kandungan TIMP 3 yang rendah dikaitkan dengan peningkatan aktiviti proteolitik MMP (Fan & Kassiri 2020). Tambahan pula, kajian oleh Takawale et al. (2017) melaporkan TIMP 3 diekspresi dengan lebih rendah didalam tisu jantung dan darah pesakit kardiomiopati iskemik.

Kajian-kajian terdahulu telah mencadangkan mekanisme daripada beberapa laluan isyarat yang mungkin menjadi asas kepada kesan merokok terhadap peningkatan MMP dalam kalangan pesakit ACS. Antaranya ialah laluan isyarat melibatkan reseptor nikotinik asetilkolina alfa-1 (α1nAChR) dan kinase terkawal isyarat ekstraselular 1 dan 2 (ERK 1/2). Kajian oleh Ren et al. (2019) menunjukkan peranan nikotin dalam meningkatkan ekspresi MMP-2 dan MMP-9 dalam sel otot licin vascular tikus (MOVAS) dan makrofaj (RAW264.7) melalui laluan isyarat α1nAChR dan calpain-1. Manakala, kajian oleh Liu et al. (2017) pula menunjukkan nikotin dengan penglibatan α7nAChR merangsang fosforilasi kinase yang dikawal oleh isyarat

ERK 1/2 dan Ap-1 untuk meningkatkan pengeluaran MMP-2 dan MMP-9 dalam makrofaj (RAW264.7). Namun, kedua-dua kajian ini menggunakan garis sel haiwan sebagai sumber MMP. Mengkaji MMP menggunakan tisu plak dan sampel darah manusia memberikan penilaian secara lansung berkaitan biologi manusia. Sampel darah meliputi sel mononuklear darah periferi (PBMC) dan serum memberikan pandangan sistemik terhadap mekanisme penyakit. Kajian oleh Jönsson et al. (2011) mendapati expresi gen mRNA MMP-9 adalah tinggi dalam PBMC dan plasma pesakit. Walau bagaimanapun, mekanisme tepat bagaimana ini berlaku, khususnya melalui laluan isyarat yang terlibat, masih belum difahami sepenuhnya. Mengkaji laluan isyarat yang memodulasi ekspresi MMP dalam PBMC boleh meningkatkan pemahaman kita tentang peranan mereka dalam patogenesis ACS dan berpotensi membawa kepada strategi terapeutik baru.

Kesimpulannya, penyelidikan ini bertujuan untuk mengupas peranan laluan isyarat α1nAChR-ERK dalam pembentukan MMP didalam sampel tisu plak aterosklerotik dan PBMC, demi memahami dengan lebih mendalam bagaimana merokok mencetuskan ketidakstabilan plak aterosklerotik dan meningkatkan risiko ACS. Rentetan itu, penyelidikan ini turut mengkaji hubungan antara MMP yang terhasil dengan keterukan penyakit dan kerosakan fungsi jantung. Dengan pemahaman ini, kita dapat mencadangkan mekanisme penyakit CAD ke arah langkah pencegahan dan rawatan yang lebih berkesan, serta memberikan peluang kepada orang ramai ke arah hidup yang lebih sihat.

1.2 PERMASALAHAN KAJIAN

Prevalens CAD didapati semakin meningkat dalam kalangan perokok lelaki, dengan ACS menjadi manifestasi klinikal yang utama. ACS lazimnya berpunca daripada kepecahan plak aterosklerotik yang tidak stabil, iaitu satu proses yang berkait rapat dengan peningkatan ekspresi MMP, terutamanya MMP-2 dan MMP-9. Enzim-enzim bersifat proteolitik ini menyumbang kepada penguraian matriks ekstraselular (ECM) dan dengan itu menjejaskan kestabilan plak aterosklerotik di dalam koronari arteri.

Kajian *in vitro* telah menunjukkan bahawa nikotin merangsang pelepasan MMP-2 dan MMP-9 melalui interaksinya dengan reseptor α1nAChR, seterusnya mengaktifkan laluan isyarat kinase yang dikawal selia oleh isyarat ERK 1/2. Namun begitu, penglibatan dan peranan laluan isyarat ini dalam meningkatkan ekspresi MMP-2 dan MMP-9 mengunakan sampel biologi manusia seperti tisu plak aterosklerotik, sel mononuklear darah periferi (PBMC) dan serum masih belum difahami sepenuhnya. Menjelaskan laluan isyarat ini adalah penting untuk memahami mekanisme molekul yang menghubungkan tabiat merokok dengan ketidakstabilan plak aterosklerotik dan perkembangan ACS.

Sehubungan itu, kajian ini turut meneliti bagaimana perubahan paras MMP berkait dengan tahap keterukan penyakir serta kemerosotan fungsi jantung. Pemahaman yang lebih mendalam mengenai hubungan ini dapat membantu menerangkan mekanisme asas patogenesis CAD, sekali gus menyokong pembangunan strategi pencegahan dan rawatan yang lebih berkesan.

1.3 PERSOALAN KAJIAN

Apakah peranan laluan isyarat α1nAChR-ERK dalam pembentukan MMP dalam plak aterosklerotik koronari dan PBMC dalam kalangan perokok lelaki dengan ACS?

1.4 OBJEKTIF KAJIAN

1.4.1 Objektif Umum

Mengkaji peranan laluan isyarat α1nAChR-ERK dalam pembentukan MMP dalam plak aterosklerotik koronari dan PBMC dalam kalangan perokok lelaki dengan ACS.

1.4.2 Objektif Khusus

i. Mengukur ekspresi gen α1nAChR, ERK 1 dan 2, dan c-FOS dalam tisu plak aterosklerotik koronari dan PBMC daripada lelaki perokok dan bukan perokok dengan ACS.
ii. Mengukur paras protein MMP-2, MMP-9, dan TIMP 3 dalam plak aterosklerotik koronari dan serum daripada lelaki perokok dan bukan perokok dengan ACS.
iii. Mengkaji perkaitan hubungan antara MMP-2, MMP-9 dan TIMP 3 dengan tahap keterukan plak aterosklerotik (skor gensini) dalam kalangan lelaki perokok dan bukan perokok dengan CAD.
iv. Mengkaji perkaitan hubungan antara MMP-2, MMP-9 dan TIMP 3 dengan parameter ekokardiografi (LVEF, E, E/A, Av E/e’ dan EDT) dalam kalangan lelaki perokok dan bukan perokok dengan CAD.

1.5 HIPOTESIS KAJIAN

i. Ekspresi gen α1nAChR, ERK 1/2, c-FOS dan paras protein MMP-2, MMP-9 dan TIMP 3 dalam tisu plak aterosklerotik koronari adalah lebih tinggi pada lelaki perokok dengan ACS berbanding lelaki bukan perokok dengan ACS.
ii. Ekspresi gen α1nAChR, ERK 1/2, c-FOS dalam PBMC dan paras protein MMP-2, MMP-9 dan TIMP 3 dalam serum adalah lebih tinggi pada lelaki perokok dengan ACS berbanding lelaki bukan perokok dengan ACS.
iii. Terdapat hubungkait di antara MMP-2, MMP-9 dan TIMP 3 dengan tahap keterukan plak aterosklerotik (skor gensini) dalam kalangan lelaki perokok dan bukan perokok dengan CAD.

iv. Terdapat hubungkait di antara MMP-2, MMP-9 dan TIMP 3 dengan parameter ekokardiografi (LVEF, E, E/A, Av E/e’ dan EDT) dalam kalangan lelaki perokok dan bukan perokok dengan CAD.

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