HUE UNIVERSITY
UNIVERSITY OF MEDICINE AND PHARMACY

CHAU MY CHI

RESEARCH OF THE CORRELATION BETWEEN PLASMA MYELOPEROXIDASE (MPO) CONCENTRATION AND CAROTID INTIMA-MEDIA THICKNESS (IMT), AND SOME CARDIOVASCULAR RISK FACTORS IN TYPE 2 DIABETIC PATIENTS

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The thesis is defended in front of the Board **HUE UNIVERSITY**
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PREFACE

Macrovascular complication is the leading cause of mortality in diabetic patients. Macrovascular complication of diabetes essentially is due to atherosclerosis. Besides the traditional atherosclerosis risk factors such as: obesity, hypertension, chronic hyperglycaemia, dyslipidemia, etc...,non-traditional risk factors such as: increased PAI-1 concentration, increased CRP concentration, micro-albuminuria and especially myeloperoxidase (MPO), a plasma leucocyte-derived enzyme, are recently reported relating to atherosclerosis in high-risk subjects, especially diabetes.

Endothelial dysfunction and an increased intima-media thickness (IMT) are early changes in the function and structure of blood vessels caused by atherosclerosis. Elevated myeloproxidase level is a pinpoint sign of endothelial dysfunction, and it also causes increasing oxidative response in diabetes. Relationship between plasma myeloperoxidase concentration and abnormal endothelial structure of peripheral blood vessels in type 2 diabetes (T2DM) has not been studied in Vietnam. From the above reasons, we implemented a research about this topic.

1. Investigating cardiovascular risk factors such as: increased carotid intima-media thickness (IMT) and elvevated plasma myeloperoxidase (MPO) concentration in type 2 diabetes (T2DM).

2. Evaluating relation and corelation between plasma myeloperoxidase level and carotid intima-media thickness, traditional cardiovascular risk factors (age, high blood pressure, and lipid disorder), and non-traditional cardiovascular risk factors (HbAlc, CRP, fibrinogen, and leucocyte...) in type 2 diabetic patients.

- Scientific and practical meanings of the study

*+ **Scientific meaning***

The study results can help to develop valid and reliable approaches in evaluating as well as predicting cardiovascular complication in type 2 diabetic patients having elevated myeloperoxidase concentration and artery injury.

The study help to identify new risk factors which contribute to proactive in treatment approach, and improve quality of life for patients scientifically in evidence-based medicine.

*+ **Practical meaning***

Contribute as the markers for diagnosis of atherosclerosis in early stage in type 2 diabetic patients who are at high risk of vascular complications.

- Contribution of the thesis

This is the first domestic thesis studying MPO concentration in patients with type-2 diabetes and the relation between the concentration of this biological marker and carotid intima-media thickness (IMT) in atherosclerosis.

The thesis provides a more comprehensive view of MPO role in atherosclerosis. The research results suggest treatment approaches to prevent further progression of atherosclerosis in patients with type 2 diabetes.

- **Structure of the thesis:**

Including 128 pages: 3 pages of opening, 38 pages of literature review, 17 pages of research objects and methods, 30 pages of research results, 37 pages of discussion, 2 pages of conclusion, and 1 page of recommendations. The thesis has 40 tables, 13 graphs, 4 charts, 15 figures, and 178 references: 41 documents in Vietnamese and 137 documents in English.

Chapter 1
LITERATURE OVERVIEW

1.1. MACROVASCULAR DISEASE IN TYPE 2 DIABETIC PATIENTS

1.1.2. Mechanism of macrovascular disease in diabetic patients

The AS (atherosclerosis) progression in type 2 diabetic patients has some characteristics such as: early occurring of vascular endothelial dysfunction, increasing platelets activity, promoting smooth muscle and substrate cells proliferation after arteries being damaged; unfavorable tendency in renewing blood vessels, damaging to the fibrin degradation with tendency of thrombosis and inflammation.

1.2. CARDIOVASCULAR RISK FACTORS IN TYPE 2 DIABETIC PATIENTS

The traditional risk factors: hypertension, dyslipidemia, and smoking…

The non-traditional risk factors: vascular endothelial dysfunction, fibrinolytic disorders, inflammation, microalbuminuria, increased blood homocysteine level, abnormal blood vessel wall- thickening intima-media, hardening vessel wall, and postprandial hyperglycemia.

1.3. MYELOPEROXIDASE (MPO) ENZYME

1.3.1. Origin, composition and physiological activity of MPO

MPO is derived from leukocytes, and has a molecular weight of about 150 kDa, including a pair of heavy chain and pair of light chain.

MPO forms HOCl from H_2O_2 and Cl. HOCl is a strong oxidative substance with antibacterial effect. However, the prolonged and frequent production of HOCl causes tissue damage and develops vascular disease.

1.3.2. The role of myeloperoxidase in atherosclerosis

1.3.2.1. Relationship between myeloperoxidase and cardiovascular diseases

The mechanism shows the role of MPO in cardiovascular disease: MPO modifies LDL into a pre-atherogenic form, causes vascular impairment, reduces biological ability of nitric oxide, and damages arteries.

MPO's role in diabetes: prolonged high glucose level in diabetes leads to metabolic disorders and oxidative stress ROS (reactive oxygen species) generation. The increase of ROS as H_2O_2; activation, adhesion and infiltration of leucocytes into the blood vessel wall are key components in the progression of vascular complications in diabetes. MPO also utilizes the oxidant H2O2, non-derived leucocyte H_2O_2, produced from high blood sugar to produce HOCl and chlorinated form.

1.4. METHODS TO EXPLORE CAROTID ATHEROSCLEROSIS INJURY

Ultrasound: carotid percutaneousultrasound, intravascular ultrasound, magnetic resonance imaging, computed tomography angiography, and digital subtraction angiography.

1.5. MYELOPEROXIDASE RELATED RESEARCHES

1.5.1. Research myeloperoxidase in cardiovascular disease

Baldus et al. in the CAPTURE research on 1,090 patients with acute coronary artery syndrome, with 6 month follow up. During the study, they observed MPO predictive values in related to mortality and acute myocardial infarction (MI) reoccurrence rate. The patients with increased MPO level have 2.25 times higher risk of re-infarction or fatality (the MPO level change does not correspond to Troponin T).

A domestic research by author Nguyen Thanh Dinh in 2011 found that the MPO concentration higher in acute MI group than the control group (p = 0.01), and there is a positive correlation between plasma MPO concetration and severity of the disease.

1.5.2. Research myeloperoxidase in diabetic pathology

Wiersma JJ studyng MPO in type 2 diabetic patients showed that the concentration of MPO is higher in diabetes vs non-diabetes (p = 0.01). This study concluded that type 2 diabetes is associated with an increased MPO level, independent with other variables in the clinic.

The research of Heilman K et al showed that diabetes has increaed MPO level (p = 0.006) and increased IMT (p = 0.005) in compared to the control group.

We have not found any domestic study related to MPO enzyme in patients with diabetes.

Chapter 2
RESEARCH SUBJECTS AND METHODS

2.1. RESEARCH SUBJECT

The participants include a type 2 diabetic group who are treated at the Internal Medicine- Tien Giang Central Hospital - and a control group.

2.1.1. The patients with type-2 diabetes group

- Diagnostic criteria for diabetes: based on 2010 ADA standard.

Diagnostic criteria for type 2 diabetes: based on 2005 International Diabetes Federation and WHO.

- Exclusion criteria: patients with severe diabetic complications which do not allow the implementation of exploration technique, and people who refuse to participate in the research.

2.1.2.The control group

Of 67 healthy people have routine check up without having diabetes or other diseases which might cause elevated MPO level. These people are also willing to participate in the research.

2.1.3. The research sites and duration

All research participants will have pre-clinical and clinical examinations at Tien Giang Center General hospital, except plasma MPO samples were sent to Hue Central hospital for testing.

Research duration : Jan, 2011- Dec, 2013.

2.2. RESEARCH METHODS

2.2.1. Design:

This was a cross-sectional research with a control group.

2.2.2. Sampling:

The quantity of subjects in patient group and in control group are calculated based on comparative formulation**.** As the result, we needed a group of 67 subjects with type 2 diabetes and 67 healthy subjects for the control group. In this sturdy, we actually studied 81 patients with type 2 diabetes and 67 healthy people.

2.3. VARIABLES

2.3.1. Traditional risk factors

These risk factors are age, sex, diabetic duration, arterial blood pressure, lipid profile, plasma atherogenic index (TC/ HDL-C, TG/HDL-C, LDL-C/HDL-C).

2.3.2. Non-traditional risk factors

- Waist line, BMI, fasting plasma glucose, HbA1c, CRP, plasma fibrinogen, neutrophils.

- Carotid IMT measurement: Mylab 50X vision ultrasound with frequency 7.5 MHz connecting to programing computer for the index calculation.

IMT rating bases on 2008 ASE guideline: IMT<0.9mm: normal; IMT ≥0.9 mm-1.49 mm: thickness of *tunica intima;* IMT ≥ 1.5mm and/or IMT > 50%: plague.

- Electrocardiography: QTc, Sokolow-Lyon index and myocardial ischemia. -Echocardiography: left ventricular mass index (LVMI), and ejection fraction (EF).

- Quantitative of plasma MPO level: Plasma was combined to EDTA anticoagulant in the immunoassay automated system ARCHITECT (Abbott) at the Department of Biochemistry- Hue Central Hospital.

+ Sample collecting, processing and storage: blood sample was placed into a tube having EDTA anticoagulant, then sent to the laboratory for plasma separation. All specimens are stored and maintained at a proper temperature (about 18^0C) during shipping to the lab at Hue Central Hospital.

2.4. COLLECTING AND PROCESSING DATA METHODS

All data was recorded on general paper-forms and transferred to SPSS 16.0 for analysis.

2.5. RESEARCH ETHICS

The research was accepted by Hue University - College of medicine and pharmacy, and Board of Directors and Scientific and Technical Council of Tien Giang Central General Hospital.

All participants were explained about the research, and agreed to take part in the research. The subject information was kept confidentially by coding and recording in computer.

Chapter 3
RESEARCH RESULT

3.1. TRADITIONAL RISK FACTORS OF RESEARCH SUBJECTS

Table 3.1. ***Allocation of age and gender rate of research subjects***

Characteristic		Patientsgroup		Control group		p
		n	%	n	%	
Sex	Male	24	29.60	19	28.36	>0.05
	Female	57	70.40	48	71.64	>0.05
	Total	81	100.00	67	100.00	
Age (years old)	<65	46	56.79	41	61.19	>0.05
	≥65	35	43.21	26	38.81	>0.05
	Average	64.22±10.52		61.64±11.49		>0.05

Age and gender of research subjects are nearly the same in both groups.

3.2. NONTRADITIONAL RISK FACTORS

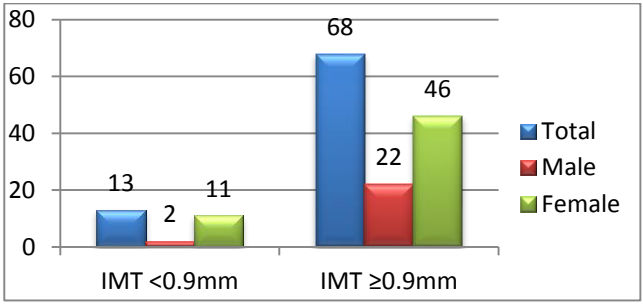

Diagram 3.2. *Rating of carotid IMT in patients group*

Diabetic patients with IMT≥ 0.9 mm accounts for 68/81 cases (83.95%): female patients account for 46/58 cases (80.7%), and male patients account for 22/24 cases (91.7%).

3.4. CONCENTRATION OF MYELOPEROXIDASE (MPO) IN SUBJECTS' PLASMA

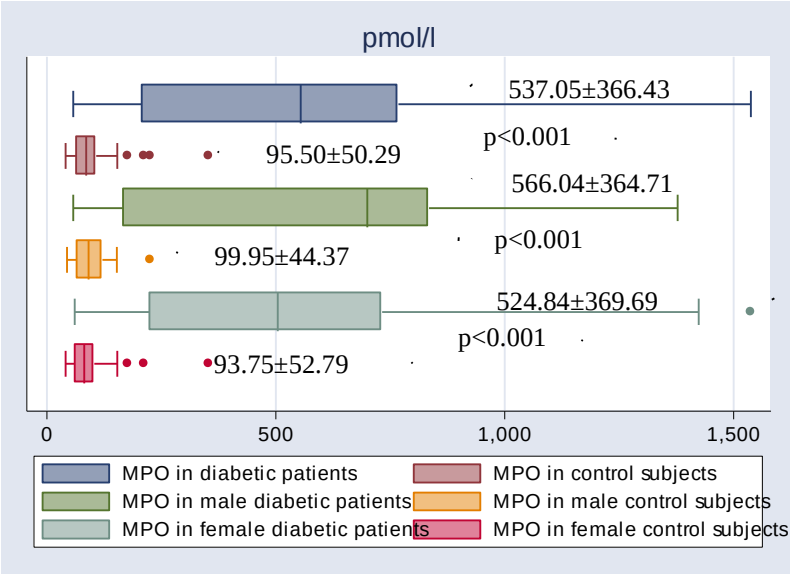

Chart 3.3.*Comparison on MPO concentration of the diabetic group with the control group*

3.5. CORRELATION BETWEEN MPO AND CARDIOVASCULAR RISK FACTORS

3.5.1. Correlation between MPO and traditional cardiovascular risk factors

Table 3.24.*Relation between MPO and age, diabetic duration and hypertension in the patient group*

Parameter	Value	MPO (pmol/l) ($\overline{X}$ ± SD)	p
Age	<55 (n=17) ≥55(n=64)	329.37±283.05 592.21±368	<0.01
Duration of diabetes	<10 years (n=65)	492.81± 372.96	<0.05
	≥10 years (n=16)	716.76 ± 282.29	
Hypertension	No (n=21)	433.67±332.26	>0.05
	Yes (n=60)	573.23±373.50	

There is a significant difference in average concentration of MPO between age groups< 55y.o vs ≥ 55y.o and duration <10 years vs ≥ 10 years, with p < 0.05.

Table 3.25. *Correlation between MPO level and lipid profile in the patient group*

Parameter	Value	MPO (pmol/l)($\overline{X}$ ± SD)	p
TC (mmo/l)	< 5.2	499.62±329.71	>0.05
	≥ 5.2	560.25± 388.87	
TG (mmol/l)	< 1.7	239.83± 212.36	<0.01
	≥ 1.7	574.20± 365.53	
LDL-C (mmol/l)	< 2.6	457.47± 348.81	>0.05
	≥ 2.6	568.61± 371.38	
HDL-C (mmol/l)	Male ≤1.01	487.55± 310.60	>0.05
	Male>1.01	658.80± 415.57	
	Female ≤1.30	471.62±328.02	>0.05
	Female>1.30	631.29±431.37	
Non-HDL-C (mmol/l)	< 3.4	417.19± 357.22	>0.05
	≥ 3.4	576.35± 363.67	
TC/HDL-C	<4	552.09±403.25	>0.05
	≥4	529.94±351.39	
TG/HDL-C	< 2.4	566.07± 371.84	>0.05
	≥ 2.4	513.83±364.56	
LDL-C/HDL-C	<2.3	560.97±387.49	>0.05
	≥2.3	524.41±357.96	

There is a significant difference in MPO level between Triglyceride< 1.7 mmol/1 and triglyceride ≥ 1.7 mmol/l, p< 0.05.

3.5.2. Relation between MPO and non-traditional risk factors

Table 3.26. *Relation between MPO level and waist line (WL) and body mass index (BMI)*

Parameter	Value	MPO (pmol/l)($\overline{X}$ ± SD)	p
WL (cm)	Normal (n=22)	476.69±361.91	>0.05
	Risk (n=59)	559.55± 368.62	
BMI (kg/m^2)	<23 (n=36)	374.66± 344.19	<0.001
	≥ 23 (n=45)	666.96± 333.24	

MPO is associated with BMI.

Table 3.28. *Relation between MPO and IMT < 0.9mm vs IMT ≥ 0.9mm*

MPO	IMT<0.9mm ($\overline{X}$ ± SD)(n=13)	IMT≥0.9mm ($\overline{X}$ ± SD)(n=68)	p
Male MPO(pmol/l)	291.90± 54.16	590.96± 371.12	<0.01
Female MPO(pmol/l)	391.75± 197.35	556.67± 395.04	>0.05
MPO for both (pmol/l)	376.38 ±184.68	567.76±385.03	<0.01

MPO is associated with IMT>0.9 mm (p<0.01).

Table 3.30. *Relation between MPO and atherosclerotic plaque*

MPO	Without plaque ($\overline{X}$ ± SD) (n=52)	With plaque ($\overline{X}$ ± SD) (n=29)	p
Male MPO (pmol/l)	327.21±303.01	736.63±310.73	<0.05
Female MPO (pmol/l)	442.15±375.88	566.19±364.39	>0.05
MPO for both (pmol/l)	402.51±351.32	612.08±356.12	<0.05

There is a significant difference in MPO concentration between atherosclerotic plaque group and non-atherosclerotic plaque group ($p < 0.05$)

3.5.3. Relation between MPO and cardiac injury on electrocardiogram

and echocardiogram

Table 3.31. *Relation between MPO and abnormal signs on electrocardiograph*

Parameter	Value	MPO (pmol/l) ($\overline{X}$ ± SD)	p
Myocardial ischemia	No	527.43±376.64	>0.05
	Yes	562.85±344.59	
QTc (ms)	<440	266.05±191.28	<0.001
	≥440	688.18±354.23	
Sokolow-Lyon (mm)	<35	536.25±343.07	>0.05
	≥35	543.42±545.99	

MPO is associated with QTc ($p<0.05$)

3.6. CORRELATION BETWEEN MPO AND OTHER RISK FACTORS

Table 3.34.*Relation between MPO and other non-traditional risk factors*

Parameter	Correlation coefficients r	p
WL (cm)	0.226	<0.05
BMI (kg/m^2)	0.242	<0.05
Blood glucose (mmol/l)	-0.017	>0.05
HbA1C (%)	0.008	>0.05
Fibrinogen (mg/dl)	0.059	>0.05
Leukocyte (G/L)	-0.048	>0.05
IMT	0.348	<0.01
Plaque	0.306	<0.01

MPO correlated positively with waist line, BMI, IMT and plaque. Linear regression function of MPO with waist line: y = 8.727x-230.5. Linear regression function of MPO with BMI:

y= 20.16x + 51.12. Linear regression function of MPO with IMT: y = 369.8x + 92.31. Linear regression function of MPO with plaque: y= 85.81x + 338.6.

Table 3:35. *Correlation between MPO with cardiac complications*

Parameter	**Correlation coefficients r (n=80)**	**p**
QTc (ms)	0.292	<0.01
Index Sokolow-Lyon (mm)	-0.160	>0.05
EF (%)	-0.163	>0.05
LVMI (g/m^2)	-0.141	>0.05

There is a positive correlation between MPO and QTc. Linear regression function y = 2.171x -482.4.

3.6.2. Correlation of multivariate linear regression

Table 3.35.*Correlation of multivariate linear regression between MPO and risk factors*

Index	**B**	**ß correction**	**T**	**P**
Constant	*-1463.974*		***-2.946***	***0.004***
WL	7.316	0.189	1.214	>0.05
BMI	8.671	0.104	0.671	>0.05
QTc	1.512	0.203	2.017	<0.05
IMT	267.975	0.252	2.146	<0.05

R= 0.52; R^2correction = 0.221.

Multivariate regression function: y=1.512 QTc+ 267.975 IMT-1463.974

There are only QTc and IMT that correlate with MPO.

3.6.3. Increased MPO predicting value in some risk factors

Table 3.36. *The area under the curve ROC between MPO and WL corresponding to MPO≥330pmol/l*

Index	Acreage (%)	Cut point	Sensitivity	The specificity	p	Level of significance 95%	
						Min	Max
WL (cm)	66.3	82.5	82%	48.4%	<0.05	53.9	78.7

When MPO ≥330 pmol/l, the optimal cutting point of waist line is 82.5cm, the area under the curve (AUC) is 66.3 %, sensitivity is 82%, specificity is 48.4 %, p<0.05.

Table 3.37. *The area under the curve ROC between MPO and BMI corresponding to MPO≥330pmol/l*

Index	Acreage (%)	Cut point	Sensitivity	The specificity	p	Level of significance 95%	
						Min	Max
BMI (kg/m^2)	70.2	23.02	72%	71%	<0.01	58.6	81.9

When MPO≥330pmol/l. the optimal cutting point of BMI is 23.02 kg/m^2, AUC is 70.2%, sensitivity is 72 %, specificity is 71%, p< 0.05.

Table 3.38. *The area under the curve ROC between MPO and IMT corresponding to MPO≥330pmol/l*

Index	Acreage (%)	Cut point	Sensitivity	The specificity	p	Level of significance 95%	
						Min	Max
IMT(mm)	63.6	1.05	68	61.3	<0.05	51.1	76.2

When MPO is more than 330 pmol/l, IMT affects the MPO concentration, the optimal cutting point of IMT is 1.05 mm; AUC is 63.6%; 95% confidence interval (CI): 51.1% - 76.2%; sensitivity is 68 %, specificity 61.3 %, p<0.05.

Table 3.39. *The area under the curve ROC between MPO and QTc corresponding to MPO≥330pmol/l*

Index	**Acreage (%)**	**Cut point**	**Sensitivity**	**The specificity**	**p**	**Level of significance 95%**	
						Min	Max
QTc (ms)	78.1	454.5	80	77.4	<0.001	66.5	89.7

When MPO concentration is more than 330 pmol/l. the optimal cutting point of QTc is 454.4ms, AUC is78.1%, sensitivity is 80%, specificity is 77.4%, p<0.05.

3.6.4. Odds ratio (OR) between MPO and some risk factors

Table 3.41. *Odds ratio between MPO and IMT*

Parameter \ **MPO**		**<330pmol/l n**	**≥330pmol/l n**	**OR**	**p**
IMT (mm)	<0.9	5	8	1.08	>0.05
	≥0.9	25	43		
Plaque (mm)	<1.5	16	13	3.02	**<0.05**
	≥1.5	14	38		

Bảng 3.42. *Odds ratio between MPO and some risk factors*

Parameter \ MPO		<330pmol/ln	≥330pmol/ln	OR	p
TC (mmol/l)	<5.2	12	19	1.12	>0.05
	≥5.2	18	32		
TG (mmol/l)	<1.7	8	1	18.18	<0.05
	≥1.7	22	50		
HDL (mmol/l)	<1	10	16	0.91	>0.05
	≥1	20	35		
LDL (mmol/l)	<2.6	11	12	1.88	>0.05
	≥2.6	19	39		
Non-HDL (mmol/l)	<3.4	12	8	3.58	<0.05
	≥3.4	18	43		
Glucose (mmol/l)	<7.2	14	14	2.31	>0.05
	≥7.2	16	37		
HbA1C (%)	<7	8	13	1.06	>0.05
	≥7	22	38		
CRP	<3	13	24	0.75	>0.05
	≥3	16	22		
Fibrinogen (mg/dl)	<400	26	35	2.97	0.05
	≥400	4	16		
Leukocyte (G/L)	<10	28	39	4.3	<0.05
	≥10	2	12		

Chapter 4
DISCUSSION

4.1. THE TRADITIONAL CARDIOVASCULAR RISK FACTORS OF RESEARCH SUBJECTS

4.1.1. Age

The average age of patient group is 64.22 ± 10.52, and control group is 61.64 ± 11.49. There is no significant difference with p> 0.05.

The average age of patient group in our research is similar with other researches about diabetes, e.g. a recent research by Tran Ngoc Hoang and Nguyen Thi Bich Dao with average age of subjects is 62.2 ± 11.0.

4.1.2. Gender

We noticed that proportion of female patients in the research predominates over male patients (71.64% vs 28.36%). In general, diabetic related studies reported a high percentage of female than male; as in the pooled analysis of Juliana C. N. Chan et al reported diabetic female were 51.9% in US, 51.4% in China, 53 .5% in Hanoi, and 74.7% in Ho Chi Minh City.

4.2. THE NON-TRADITIONAL CARDIOVASCULAR RISK FACTORS OF RESEARCH SUBJECTS

4.2.3. Blood glucose and HbA1C

The average blood glucose level in our subjects is 9.36 ± 4.14 mmol/l. The proportion of patients that achieved the target glycemic control is 34.6%, and did not achieve the target is 65.4%.

The average HbA1C is 8.92 ± 2.42. The proportion of patients that reach HbA1C target is 25.9%, and did not reach the target is 74.1%. The research results showed that the majority did not reach the treatment goals as recommended.

4.2.7. Carotid intima-media thickness (IMT)

We recorded the carotid IMT in T2DM is 1.20 ± 0.35 mm. Males with IMT ≥0.9mm account for 83.95% (22/24 cases) and (46/57 cases) in females.

The carotid IMT in our research is similar to a recent research by Yoko Ire (2013) in 333 T2DM which is 1.05 ± 0.42mm. Moatassem S. Amer Authors (2014), IMT is 1.14 ± 0.2 mm in 58 T2DM which is higher than IMT in 59 control subjects (0.69 ± 0.2 mm), p <0.001.

4.4. MPO CONCENTRATION IN RESEARCH SUBJECTS

4.4.2. Compare the MPO concentration between diabetic group and control group

MPO concentrations of diabetic group is significantly higher than control group (537.05 ± 366.43 pmol/l vs. 95.50 ± 50.29 pmol/l, p <0.01). Plasma MPO concentrations by gender in both groups also has significant differences (p <0.001). Our research results are consistent with results of related researches from authors in other countries.

Joseph A. Vita et al (2004) reported that diabetic patients with intima dysfunction have an increasing MPO concentration 573 pmol/l in compared to 253 pmol/l in patient without intima dysfunction (p <0.001).

Study of Andrey Eu. Kratnov et al (2014) showed that MPO concentration relates to the risk of developing type 2 diabetes. Patients with metabolic syndrome have higher MPO level and higher chance of developing diabetes in 10 years (Findrisk scale ≥15) in compared to lower risk groups (Findrisk scale <15), p = 0.01.

4.5. THE CORRELATIONS BETWEEN THE PLASMA MPO CONCENTRATION WITH CARDIOVASCULAR RISK FACTORS

4.5.1. The correlations between the MPO and traditional risk factors

4.5.1.1. The correlation between the MPO and age

MPO concentration in two age groups <55 and ≥55 statistically has significant difference (329.37 ± 283.05pmol/l vs. 592.21 ± 368pmol/l, p <0.01). Our research is consistent with Wiersma (2008) which showed that the concentration of MPO in T2DM is higher than the control group and relates to the age.

4.5.1.2. The correlation between the MPO and gender

In our research, we found that MPO concentration does not associated with gender. Wiersma et al (2008) also noted that concentration of MPO in T2DM does not related to gender and HbA1C.

4.5.1.3. The correlation between the MPO and diabetic duration

In our research, less than 10 year diabetic patients have lower MPO concentration (492.81 ± 372.96 pmol/l) than 10 and more than 10 year diabetic patients (716.76 ± 282.29 pmol/l), p <0.05.

Shankar Shetty et al (2012) also found that MPO related to diabetic duration.

4.5.1.5. The correlations between the MPO and dyslipidemia and atherogenic index

We recorded lower MPO concentration in the normal triglycerides group and higher MPO concentration in the risk group (239.83 ± 212.36 pmol/l vs. 365.53 ± 574.2 pmol/l, p<0.01).

The result of our research is consistent with the result of Vita in which MPO level relates to diabetes, age, and triglycerides.

Researches showed that type 2 diabetic patients with increasing triglycerides have MPO level increased, therefore have higher risk of atherosclerosis.

4.5.2. The correlations between the MPO and non-traditional risk factors

4.5.2.1. The correlation between the MPO and body mass index

We noted that MPO concentration is 374.66 ± 344.2 mmol/L in subjects with BMI < 23kg/m^2 and is 666.96 ± 333.25 mmol/L in subjects with BMI > 23kg/m^2. The difference is statistically significant (p = 0.001).

Nathan D Wong et al (2009) also recorded significant difference of MPO levels: MPO <257pmol/l (n = 649) and MPO≥257pmol/l (n = 653) in 2 groups with BMI 28.6 ± 4.7 and 26.6 ± 5.7 respectively, p <0.0001, in a 3.8 year study.

Josune Olza et al (2012) recorded the difference in the concentration of MPO in nonobese group and obese group with p <0.001.

4.5.2.5. The association between MPO and carotid IMT

From the result analysis about the relation between concentration of MPO and carotid IMT, we recorded significant differences in plasma MPO concentration between the two groups: IMT <0.9 mm and IMT ≥ 0.9 mm (376.38 ± 184.68pmol/l vs. 567.76 ± 385.03 pmol/l, p <0.01). The difference exists in both genders but is significant in men (p <0.01).

We also recorded the MPO concentration is significantly higher in the group with plaque than the group without plaque (p <0.05).

Heilman K. et al (2009) studied 30 patients with diabetes and 30 healthy people. Finding results showed that the diabetic group has increasing MPO concentration and IMT in compared to the control group with p = 0.006 and p = 0.005 respectively.

YuKataoka et al (2014) observed that the elevated MPO level relates to progression of atherosclerosis in diabetic patients. They studied 881 patients with coronary artery disease -confirmed by coronary angiography- in which 199 patients are diabetic, and 682 patients are nondiabetic. Both groups have similar initial MPO levels. The severity of atherosclerosis was monitored and evaluated by intravascular ultrasound. The research results showed a correlation between increasing MPO concentration and atherosclerosis progression in diabetic group.

4.5.3. The correlations between the MPO and cardiac injury through Electrocardiograms and echocardiography

4.5.3.1. The correlations between the MPO and myocardial ischemia on QTc and Sokolow-Lyon index

The correlations between the MPO and QTc

MPO concentrations between 2 groups with QTc<440ms and QTc≥440ms in our research have significant differences (266.05 ± 191.28pmol/l in compared to 688.18 ± 354.23 pmol/l, p <0.001).

Currently, we have not found documents about correlation between MPO and QTc in patients with type 2 diabetes. Regarding MPO and electrocardiogram study, we found a research of Rudolph et al. showed that the patients with atrial fibrillation have higher MPO concentration than those without atrial fibrillation. The authors believe that inflammation response in cardiac repair increases cardiac vulnerability and leads to atrial fibrillation.

4.6. THE CORRELATION BETWEEN MPO AND RISK FACTORS

4.6.1. The simple regression correlation between MPO and the risk factors

The simple regression correlation between MPO and the risk factors results in our research showed a positive correlation between the MPO and waistline, BMI, IMT, plaque and QTc.

The correlation between the MPO and waist line is r = 0.226, p= 0.043, simple linear regression equation: y = 8.727x-230.5.

The correlation with BMI is r = 0.242, p = 0.030, simple linear regression equation:

y = 20.16x + 51.12.

The correlation with IMT is r = 0.34, p <0.01, simple linear regression equation:

y = 369.8x + 92.31.

Josune Olza (2012) also recorded that the MPO concentration had significantly correlation with waistline and BMI, with correlation r = 0.108 and r = 0.155 respectively, p <0.05.

Fu Li Juan (2007) studied 120 patients with metabolic syndrome who was diagnosed according to 2005 IDF criteria. The study recognized that patients with the metabolic syndrome have increased both plasma MPO level and IMT. MPO correlated with IMT with correlation r = 0.0213, p <0.05. Similar results from the research of Li Tao (2008) in 90 patients with metabolic syndrome showed that MPO correlates with IMT, the correlation r = 0.241, p = 0.022.

Other related researches also showed a positive correlation between the MPO level and the presence of plaque.

Krasniak and his partners (2007) recorded MPO concentration correlating with carotid artery plaque with the correlation r = 0.24, p <0.05 in the simple analysis.

Markus Exner (2006) also found that MPO correlated with carotid stenosis with r = 0.083, p = 0.008.

In our research, MPO correlates with plaque with a correlation r = 0.306, p = 0.005. We recorded a positive correlation between QTc and MPO in T2DM, with r = 0.292, p <0.01, simple linear regression equation: y = 2.171x-482.4

4.6.2. The multivariate regression correlation between the MPO and the risk factors

To evaluate the multivariate correlation between the MPO and correlated factors with MPO like waist line, BMI, QTc, and IMT. We analyzed the multivariate correlation between the MPO with the above factors. Results of multivariate regression analysis showed that QTc and IMT had significant impact on MPO (p <0.05) with adjusted waist size and BMI, multivariate regression equation is: y = 1.512QTc + 267.975IMT-1463.974.

4.6.3. The ROC curve and odds ratio

To assess the elevated MPO level as a predictive value of correlated factors with MPO, we found that:

When corresponding at intersection MPO ≥ 330 pmol/l, waist line is a factor affecting MPO concentration at optimal point of 82.5 cm with AUC is 66.3%, sensitivity is 82 %, specificity is 48.4%, p <0.05

When corresponding at intersection MPO≥330pmol/l, BMI affects the MPO concentration at optimal point of 23.02 kg/m2 with AUC is 70.2%, sensitivity is 72%, specificity is 71%, p <0.01

At the cutting point MPO ≥ 330 pmol/l, IMT affects the MPO concentration at optimal point of 1.05 mm with AUC is 63.6%, sensitivity is 68%, specificity is 61.3%, $p<0.05$

At the cutting point MPO≥ 330pmol/l, AUC between MPO and QTc is 78.1% with optimal cutting point of QTc is 454.5ms, sensitivity is 80%, specificity is 77.4%, $p < 0.01$

We noticed that MPO≥330pmol/l associates with 1.07 times higher chance of having IMT≥0.9mm (OR=1.07; 95%CI: 0.38-2.96) and 3.34 times for atherosclerosis (OR=3.34; 95%CI: 1.28-8.67).

In relation with blood glucose, MPO≥330pmol/l associates with BG ≥ 7.2 mmol/l, 2.31 times higher risk (OR=2.31; 95%CI: 0.89-5.95) and HbA1C≥7%, 1.31 times higher risk (OR=1.31; 95%CI: 0.38-2.96).

In relation with lipids, MPO≥330pmol/l associates with total cholesterol TC ≥5.2mmol/l, 1.12 times higher risk (OR=1.12; 95%CI: 0.44-2.83) with triglyceride≥1.7mmol/l, 18.18 times higher risk (OR=18.18; 95%CI:2.14-154.3%) with LDL-cholesterol≥2.6mmol/l, 1.88 times higher risk (OR=1.88; 95%CI: 0.7-5.03), and 3.58 times higher risk (OR=3,58; 95%CI:1,25-10,24) with nonHDL-TC≥3.4mmol/l.

In relation with inflammatory factors such as CRP, fibrinogen, and leucocytes, MPO≥330pmol/l associates with CRP insignificantly (OR<1), but significantly with fibrinogen, 2.97 times higher chance (OR=2.97; 95%CI:0.88-9.93) and leucocye, 4.3 times higher chance (OR=4.3; 95%CI:0.89-20.78).

CONCLUSION

1. Identifying reasons for cardiac risk factors, carotid intima-media thickness and blood plasma myeloperoxidase concentration on type-2 diabetic patients.

- Some cardiovascular risk factors: Average age of the subjects is 64.22±10.52 with higher percentage of women than men (70.4% vs. 29.6%). Hypertension accounts for a high proportion (74.1%). Low number of subjects achieve the lipid goal (Triglycerid: 11.1%; NonHDL-C: 24.7%; LDL-C: 28.4%; HDL-C: 37%; Cholesterol: 38.3%). The proportion of overweight and obesity accounts for 55.6%. Abdominal obesity accounts for 71.8%. Poor blood glucose control accounts for 65.4%. Number of unachieved HbA1C target subjects remains high, which accounts for 74.1%.

- Carotid IMT: Carotid IMT average is 1.20 ± 0.35mm with 83.95% of cases having IMT ≥0.9mm. Patients with plaque account for 64.2%.

- MPO concentration: MPO level in diabetic patients is higher than the control group (537.05 ± 366.43 pmol/l in compared to 95.50 ± 50.29pmol/l, $p < 0.001$). There are 61diabetic patients (75.3%) with MPO≥196.08 pmol/l which is more than the control group (4.5%), $p < 0.001$.

2. Evaluating relation and corelation between blood plasma myeloperoxidase cencentration and carotid intima-media thichkness and some cardiac risk factors on the diabetic patients type-2

- Relations: There is a relation between plasma MPO concentration with normal and pathology carotid IMT (567.76 ± 385.03 pmol/l compared to 376.38 ± 184.68 pmol/l. $p < 0.01$). There is a relation between the plasma MPO concentration and age, duration of diabetes detection, the concentration of triglycerides, BMI, QTc and plaque ($p < 0.05$).

- Correlations: There is a correlation between plasma MPO concentration and IMT ($r = 0.348$, $p < 0.01$, and $y = 369.8x + 92.31$), plaque ($r = 0.306$, $p < 0.01$), waist line ($r = 0.226$, $p < 0.05$, and $y = 8.727x-230.5$), BMI ($r = 0.242$, $p < 0.05$, and $y = 20.16x + 51.12$), and QTc ($r = 0.292$, $p < 0.01$, and $y = 2.171x-482.4$) on analysis of univariate liner regression.

- Analysis of multivariate linear regression: MPO correlated with IMT and QTc ($\beta = 0.252$ and β calibration correction = 0.203, $p < 0.05$, and $y = 267.975 + 1.512$ IMT QTc-1463.974) after adjusting waist factors ($\beta = 0.189$, $p > 0.05$) and BMI ($\beta = 0.104$, $p > 0.05$).

- At the cutting point MPO $\geq$ 330 pmol/l, found the cutting point of IMT is 1.05 mm; waist line is 82.5 cm; BMI is 23.02 kg/m^2 and QTc is 454.4ms.

RECOMMENDATION

1. The research recognized that increased plasma MPO concentration in type 2 diabetic patients is relatively popular and currently is considered as one of biological markers of atherosclerosis. This biomarker should be added to Bilan complication of type 2 diabetic patients and the necessary to have more detail and positive treatment.
2. The increase of plasma MPO concentration on type-2 diabetic patients relates to the thickness of IMT and carotid artery atheroma. Therefore, when MPO concentration increases, carotid artery studies help to detect asymptomatic carotid artery disease for early intervention, especially when MPO concentration is greater than 330pmol/1.
3. The research also shows that the increase of MPO concentration relates to prolonged QTc on electrocardiogram which reflects injury of cardiac muscles the same as in cardiovascular complication due to the increased plasma MPO concentration. Especially, the increase of this concentration relates to triglycerides, waist size, and BMI. These can be the risk factors of increased plasma MPO concentration. Thus, it requires effective strategies and approaches to manage these factors in type 2 diabetic patients.

LIST OF RELATED SCIENTIFIC RESEARCHES PUBLISHED

1. Nguyen Hai Thuy. Chau My Chi. Dao Thi Dua (2012). "The value of plasma myeloperoxidase concentration in predicting silent atherosclerotic lesions intype-2 diabetic patients".*Journal of Endocrine-Diabetes*. number 7. p.396-404.
2. Nguyen Hai Thuy. Vo Bao Dung. Chau My Chi (2012). "The non-traditional cardiovascular risk factors in type-2 diabetic patients".*Medical Practice*. episode 800. p.33-55.
3. Chau My Chi. Nguyen Hai Thuy. Dao Thi Dua (2013). "Role of myeloperoxidase in the pathogenesis of atherosclerosis in type-2 diabetic patients ".*Journal of Medicine and Pharmacy*. p.61-66.
4. Chau My Chi. Nguyen Hai Thuy. Dao Thi Dua (2013). "The non-traditional cardiovascular risk factors in type-2 diabetic patients".*Journal of Medicine and Pharmcy*. p.67-71.
5. Chau My Chi. Nguyen Hai Thuy. Dao Thi Dua (2013). "The techniques exploring atherosclerotic lesions".*Journal of Medicine and Pharmcy*. p.72-76.
6. Chau My Chi. Nguyen Hai Thuy. Dao Thi Dua (2013). "Correlation between myeloperoxidase (MPO) plasma concentraition with carotid initia media thickness and a number of cardiovascular risk factors in type-2 diabetic patients ".*Journal of Medicine and Pharmcy- Hue College of Medicine and Pharmacy*. episode 15. p.186-194.