行政院國家科學委員會補助專題研究計畫期末報告

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※ **糖尿病對頸動脈構造及功能之影響** ※
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計畫類別：□個別型計畫　　□整合型計畫

計畫編號：NSC 90－2320－B－002－178－

執行期間：90 年 08 月 01 日至 91 年 07 月 31 日

計畫主持人：蘇大成　醫師

共同主持人：鄭建興　醫師

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□國際合作研究計畫國外研究報告書一份

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行政院國家科學委員會補助專題研究計畫期末報告

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一、中文摘要

研究背景：糖尿病是冠狀動脈心臟病及腦中風之主要危險因子。近年隨著經濟發展生活富裕，國人常有營養過度及肥胖之趨勢，國人糖尿病的盛行率有逐年上昇之勢，糖尿病對國人健康的威脅絕不可忽視。材料及方法：本研究藉由具人群代表性的社區心臟血管研究--金山社區長期追蹤的族群中，使用病例對照組於1994-1995 年金山社區第三次追蹤的世代中，空腹血糖超過 126mg/dl 者，或是有糖尿病病史正在接受治療者，其年齡現在在 45-65 歲者共 192 位，選為病例組，而經由性別及年齡配對後，選出對照組 192 位，總共 384 位納入此次研究通知對象。我們用高解析度的 B 模式的頸動脈超音波來測量，並以總頸動脈最厚的內皮+中皮厚度(IMT)，及顱外頸動脈硬化塊分數，來表示顱外頸動脈硬化的程度及頸動脈血管直徑大小在收縮期及舒張期的變化來看頸動脈彈性。。結果：於 2001 年共有 108 位有糖尿病病史及 135 位對照組參與頸動脈硬化及彈性之檢查。我們發現糖尿病患者頸動壁脈增厚及動脈硬化塊的嚴重程度與對照組並無顯著差異，但頸動脈血管彈性則明顯變差。即使用多變項迴歸分析來檢驗頸動脈血管彈性指標，我們用擴張參數(distensibility coefficient, DC)來表達時，發現糖尿病病史、年齡、收縮壓、平均動脈壓、脈壓差皆是擴張參數的重要影響因子。結論：糖尿病明顯的影響頸動脈的動脈彈性。我們的發現更加強了糖尿病在動脈硬化的病理形成上扮演一主要的角色的理論。

二、英文摘要

Backgrounds： With the current trend of aging population in Taiwan, it is urgent to pay more attention to early detection of atherosclerosis to prevent the atherosclerotic diseases. Diabetes mellitus (DM) is one of the well- known and major risk factors for coronary and carotid arteries atherosclerosis. **Material and Methods：** One hundred and eight DM patients and 135 non-DM control subjects from the Chin-Shan Community Cardiovascular Cohort participated in this study in 2001. The carotid atherosclerosis was measured by high-resolution B-mode ultrasonography and expressed as maximal intima-media thickness of the common carotid artery (CA), internal CA, carotid

bulb, and extracranial CA plaque score. The carotid arterial compliance was measured using common CA diameter changes, and was defined as Distensibility Coefficient (DC)= (2(systolic diameter - diastolic diameter)/ systolic diameter)/(systolic BP-diastolic BP). Results of measurements of carotid atherosclerosis showed no significant difference between DM and control. However, DC decreased in DM group while comparing with control. Further analysis using multivariate lineal regression model revealed that DM, age, blood pressure components (SBP, DBP, MAP, and PP) are important determinants of DC. **Conclusions：** Patients with DM decreased carotid arterial distensibility though no significant difference in carotid atherosclerosis. Our findings support that DM is important in the pathogenesis of atherosclerosis in middle-aged population.

三、研究背景及緣由 Backgrounds and Introduction

Studies have shown that atherosclerosis related diseases such as stroke, cardiovascular disease (CVD) and diabetes mellitus (DM) have ranked as the second, fourth and fifth leading cause of death in Taiwan [1]. With the current trend of aging population in Taiwan, it is therefore urgent to pay more attention to prevent the atherosclerotic diseases. More significantly, early detection of atherosclerosis and its associated risk factors is a must to prevent the occurrence and progression of these diseases.

This research was designed to demonstrate the relationships between DM and carotid arterial compliance, and carotid atherosclerosis. The carotid ultrasound will be used to detect atherosclerosis and carotid compliance. Carotid ultrasound is reliable, reproducible and non-invasive technique that allows easy measurement of the overt atherosclerosis in the carotid arteries [2-4] that is strongly associated with cardiovascular risk factors [5-7], and cardiovascular morbidity and mortality [8-9]. We also had demonstrated in CCCC study in Taiwan that hypertension is the major determinant for carotid atherosclerosis [7].With the aging of the population and the increasing prevalence of obesity that might lead to an increasing prevalence of DM and thereby atherosclerosis, present study will be of significant in early detection the abnormalities in carotid arteries of DM patients.

四、材料與方法 Materials and Methods

Subjects

The Chin-Shan Community Cardiovascular Cohort (CCCC) Study is a prospective and longitudinal study that evaluates the incidences, prevalence, mortality and risk factors of cardiovascular and cerebrovascular diseases in a northern Taiwan community since 1990 [7,10-12].

In present study, we will recruit patients with diabetes mellitus and fulfill the criteria of history of diabetes mellitus or fasting blood sugar ≥126 mg/dl from the third biennial follow-up in 1994-1995 from the CCCC Study. One hundred and ninety two with DM aged 45-64 will be chosen as cases and another 192 control were randomly selected from non-diabetes frequency matched for gender and age. Home-visit or telephone will contact all participants. After obtaining inform consent, participants will be arranged for atherosclerosis measurements.

Arterial Stiffness and Atherosclerosis Assessments

1. Arterial stiffness

High resolution 2-D, M-mode, and pulse-Doppler ultrasonography will be used to measure the following parameters at bilateral extracranial carotid arteries for each participant. The following methods will be used for carotid arterial stiffness measurements [13].

(1). Vascular wall stiffness (β) = ln (Ps/Pd)Dd / (Ds-Dd) [14]. (2). Distensibility Coefficient (DC)=(2(Ds-Dd)/Ds)/(sbp-dbp) (3). The pulsatility index (PI)= (peak systolic velocity -end diastolic velocity) / mean velocity (4). Resistance index (RI)= (peak systolic velocity -end diastolic velocity) / peak systolic velocity.

2. Carotid Atherosclerosis

Carotid Artery Intima-Media Thickness (IMT)

The maximal IMTs on the common carotid artery (CCA), bulb, and internal carotid artery (ICA) bilaterally will be measured using high-resolution B-mode ultrasonography. A Hewlett Packard SONO 4500 ultrasound system (Andover, MA, U.S.A.), equipped with a 10.0 MHz real-time B-mode scanner and a 5.6 MHz pulsed-Doppler mode scanner, will be used for evaluation. We had studied the reliability of repeat measurements of CCA IMTs according to the inter-observer and intra-observer groups in previous study. The inter-observer correlation coefficients were 0.80 to 0.93 and the intra-observer correlation coefficients were 0.71 to 0.90 [15].

Extracranial Carotid Atherosclerotic (ECCA) Plaque

The plaque scoring quantified method has been mentioned elsewhere [7,16]. In this study, the examination will include the proximal CCA (>20 mm proximal to the bulb bifurcation), distal CCA, bulb, internal carotid artery, and external carotid artery bilaterally. The plaque score will be computed by summing the plaque grades at each of the segments of the ECCA.

The velocity criteria and the real-time B-mode images will be used to assess carotid stenosis. Carotid stenosis ≥50% will be also defined in the presence of peak systolic velocity ≥1.25 m/s. Reproducibility of plaque grade scoring showed perfect agreement with kappa value of 0.701 in our previous study.

Assessment of Vascular Risk Factors

BP measurements were performed with mercury sphygmomanometer in a standardized fashion cuff size adjusted to the circumference of the arm. BP was recorded using the means of two measurements taken after 5 minutes of rest in the supine position. Data on alcohol use and smoking were obtained by self-reported questionnaire. DM was defined as fasting serum glucose ≥126mg/dl in at least two different measurements and/or a history of use of medication.

Lipid and Lipoprotein Assays

Blood samples of 9-12 hours overnight fasting for lipid and glucose determination were drawn from antecubital vein with patient in a seated position. Serum levels of lipid profiles, including total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides, Apolipoprotein (Apo) A1 and B were analyzed in a central laboratory and described previously [7,10-12].

Statistical Analyses

In the data analysis, clinical features and cardiovascular risk factors of study subjects were compared between DM and control. Continuous variables are expressed as the mean ±1 standard deviation. Chi-square tests was used to make comparisons between two groups. The average carotid artery IMT measurements at CCA, bulb, ICA on both sides were compared between DM and control. The total scores of ECCA plaques were compared also between DM and control. Multivariate lineal regression analysis was used to test the significant predictors for carotid arterial distensibility, which expressed as DC.

五、結果 Results

Table 1 showed that obesity indexes and fasting sugar were the major difference between groups of DM and control. There were no significant difference regarding other CV risk factors. Table 2 showed the measurement of carotid atherosclerosis in DM had no significant difference compared with control. Carotid arterial compliance parameters expressed as DC and β decreased in DM patients while compared with control in Table 3. The multiple regression model was used to find out the significant determinants of carotid arterial DC in Table 4. Results revealed diabetes, aged, and blood pressure components (SBP, DBP, PP, and MAP) were predictors of DC.

六、討論 Discussions

Atherosclerosis shares an important role in the development of coronary heart disease and stroke, and DM is one of the well- known and major risk factors for coronary and carotid arteries atherosclerosis. Recent studies have shown that DM in Taiwan have a higher prevalence rate as compared with the Western countries and the rate is progressively increased in aged over 35 [12]. In addition, one line of research has demonstrated that the incidence rate, based on the United State population standardized non-insulin dependent diabetes mellitus (NIDDM), is 9.3/1000 for men and women in Taiwan[4]. Studies have shown that the fasting glucose level, a symptom of establish diabetes, is associated with common carotid artery (CCA) intima-media thickness (IMT) that may suggest a chronic hyperglycemia and metabolic abnormalities and sequentially an increased risk for atheroscelerosis [18-19].

In pathophysiological mechanism, obesity was considered as an important trigger factor of diabetes[7]. It is also a significant risk factor for cardiovascular disease (CVD), and is especially at higher risk for overweight men and women [20-21]. Due to the obesity associated multiple worse metabolic effects on CVD and its undeviating association with CVD, the American Heart Association (AHA) has claimed obesity as a major CVD risk since 1998 [22]. Body mass index (BMI) was proposed as a reliable indicator for assessing abdominal obesity and surrogate for CVD in most population.

In our preliminary work, we found that BMI presented in the case of obesity was significantly associated with dyslipidemia (increased cholesterol, LDL-C, TG, and Apo-B) in the female cohort [11]. In addition, hyperinsulinemia was also associated with higher BMI and dyslipidemia was presented in both gender. Our results showed that obesity was associated with relative risk of 5.5 for hyperinsulinemia [13]. Obesity also is one of presentation of insulin resistance syndrome[23]. Diabetes and hyperinsulinemia may be considered as an important risk, a metabolic syndrome with detrimental effects on dyslipidemia and carotid artrial compliance.

In conclusions, patients with DM decreased carotid arterial distensibility though no significant difference in carotid atherosclerosis. Our findings support that DM is important in the pathogenesis of atherosclerosis in middle-aged population.

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Table 1 Baseline Characteristics of Participants.

Characteristics	DM (N=108)	Non-DM (N=135)	p-value
Age, yrs	55.5±5.53	55.6±5.51	0.8156
Male, %	54.6%	48.1%	0.3148
BMI, kg/m^2	25.9±3.78	24.9±4.92	0.0661
WHR, %	0.93±0.065	0.89±0.067	0.0001
SBP, mmHg	128.1±17.7	124.4±17.2	0.1059
DBP, mmHg	83.2±12.3	81.7±12.7	0.3390
Smoking, %	25.26%	25.21%	0.9929
Alcohol, %	12.77%	21.19%	0.1086
ECG_LVH, %	14.81%	10.37%	0.2953
CAD, %	2.47%	4.08%	0.5508
CVA; %	3.77%	0.76%	0.1748
AC Sugar, mg/dl	163.8±59.7	100.9±9.4	<0.0001
Cholesterol, mg/dl	213.1±54.3	205.2±40.2	0.2152
Triglyceride, mg/dl	191.3±119.2	166.8±176.2	0.2116
HDL, mg/dl	45.8±21.3	45.3±13.4	0.8412
LDL, mg/dl	131.7±50.6	125.9±37.3	0.3288
ApoA1	1.47±0.38	1.47±0.34	0.9039
ApoB	0.67±0.17	0.63±0.18	0.0981
UA	7.55±2.39	7.27±2.12	0.3452

Data are expressed as Mean± SD, or percentages in the subgroup.

Table 2 Measurements of Carotid Arteriosclerosis

	DM (N=108)	Non-DM (N=135)	p-value
IMT, cm			
CCA	0.088±0.021	0.086±0.022	0.4604
Bulb	0.100±0.036	0.094±0.033	0.1702
ICA	0.076±0.022	0.094±0.033	0.2672
MEAN	0.088±0.022	0.085±0.020	0.1723
ECCA Plaque Score			
Total Score	1.500±2.646	1.119±2.133	0.2257

Data are expressed as Mean±SD.

Table 3. Measurements of Carotid Arterial Compliance

	DM(N=108)	Non-DM(N=134)	p-value
Ds, cm	0.65±0.06	0.63±0.09	0.0138
Dd, cm	0.60±0.06	0.57±0.08	0.0019
PI	1.29±1.30	1.20±0.33	0.3355
RI	0.66±0.07	0.65±0.07	0.1055
DC, $mmHg^{-1}$	0.0038±0.0014	0.0046±0.0025	0.0028
Â	5.40±2.16	4.79±2.02	0.0236

Data are expressed as Mean±SD.

Distensibility Coefficient (DC)=(2(Ds-Dd)/Ds)/(sbp-dbp)

â=(log(sbp/dbp))×(Dd/(Ds-Dd))

Table 4. Multiple Regression Analysis for Distensibility Coefficient (DC) of Common Carotid Artery Compliance with Respect to Associated Risk Factors.

Variables	Distensibility Coefficient					
	Model 1		Model 2		Model 3	
	PE, 10^{-3}	P	PE, 10^{-3}	p	PE, 10^{-3}	p
Intercept	11.03	0.0001	10.57	0.0001	12.04	0.0001
Diabetes	-0.68	0.0133	-0.68	0.0129	-0.75	0.0103
Age, years	-0.055	0.0290	-0.054	0.0314	-0.088	0.0009
Male	0.058	0.8563	0.043	0.8920	0.080	0.8144
SBP, mmHg	-0.074	0.0001	—	—	—	—
DBP, mmHg	0.068	0.0001	—	—	—	—
PP, mmHg	—	—	-0.075	0.0001	—	—
MAP, mmHg	—	—	—	—	-0.029	0.0089

＊ Model 1 :R^2=0.2277, adjusted R^2=0.1936 .
Model 2 :R^2=0.2265, adjusted R^2=0.1963 .
Model 3 :R^2=0.1129, adjusted R^2=0.0782 .

＊ All models expressed after adjusted for current smoking, body mass index, low-density lipoprotein cholesterol(LDL), and high-density lipoprotein cholesterol(HDL).

＊ Abbreviations: PE, parameter estimate; PP, Pulse Pressure, PP=SBP-DBP; MAP, Mean attery pressure, MAP=(SBP+2DBP)/3 .