行政院國家科學委員會專題研究計畫 成果報告

利用多探頭電腦斷層攝影探究胰島素增敏劑對合併胰島素阻抗之冠心病患改善冠狀動脈鈣化程度及班塊脆弱度及體積之影響

研究成果報告(精簡版)

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計 畫 主 持 人：王宗道
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行政院國家科學委員會補助專題研究計畫 ■ 成 果 報 告 □期中進度報告

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成果報告類型(依經費核定清單規定繳交)：■精簡報告　□完整報告

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執行單位：國立台灣大學醫學院內科

中　華　民　國　96 年　10 月　29 日

中文摘要：

關鍵詞：電腦斷層，冠心病，胰島素阻抗，胰島素增敏劑，動脈硬化斑塊

背景：第二型糖尿病及其前期狀態的代謝症候群（metabolic syndrome）均為引發動脈硬化疾病的重要危險因子。然而，使用傳統的降血糖藥物，不論是體外給予胰島素或使用刺激體內分泌更多胰島素的藥物，儘管能將血糖的數值降低，卻無法顯著降低這類病人未來發生心血管疾病的危險性。另一方面，吾等及其他研究者使用新進發展出的胰島素增敏劑（thiazolidinedione）治療第二型糖尿病或非糖尿病的代謝症候群病人均顯示其具有防治動脈硬化進展的作用。近來的研究顯示，會造成臨床上冠狀動脈疾病發作的動脈硬化病變，其多半並未造成厲害的血管管徑狹窄，然卻具有不穩定的易破裂特性（稱之為『脆弱斑塊』）。新進發展的 16/64 陣列多探頭電腦斷層檢查（MDCT）是目前唯一能以非侵入式方式探測冠狀動脈硬化斑塊組織特性的檢驗工具。在本研究中，我們將利用系列的 MDCT 檢查，探討使用胰島素增敏劑對於第二型糖尿病及非糖尿病代謝症候群病人同時患有冠狀動脈硬化疾病者，其冠狀動脈硬化斑塊的體積及組織特性變化，每位受試者預計追蹤兩年。

實驗方法及結果：病患年齡在十八歲以上，符合第二型糖尿病診斷或美國 NCEP 診斷代謝症候群條件且有心肌缺氧者，均先接受 MDCT 冠狀動脈攝影，傳統冠狀動脈攝影及介入治療（若臨床必須），及血管內超音波檢查（若 MDCT 發現有非阻塞性動脈硬化斑塊）。若病患確有無須/未經介入治療之非阻塞性（管徑狹窄程度≥20%及<70%）動脈硬化斑塊，即可進入本試驗。病患以 1:1 之比例隨機分配為接受 pioglitazone （30 mg/day）及安慰劑兩組。第二型糖尿病患分配至安慰劑組者原則上不能接受 thiazolidinedione 類藥物治療。所有第二型糖尿病人的血糖治療標的均是將 HbA1C 降至≤7%。本研究總計收錄 120 位病患，每位病患追蹤兩年。為了評估冠狀動脈硬化變化，所有的受試者均於進入研究時、(第三)、六、十二、及二十四個月接受 MDCT 冠狀動脈攝影掃描。血液樣本亦將於 MDCT 時採集，分析各種傳統及嶄新危險因子，及基因型態。本研究的主要分析項目（primary end-points）為斑塊總體積的變化，斑塊性質（CT 密度值及其他型態特徵）的改變，及總鈣化指數的變化。次要分析項目（secondary end-points）為個別冠狀動脈血管的鈣化指數變化，心外脂肪層（epicardial fat）量的變化，血中血糖、胰島素、HOMA 指數、及其他危險因子的濃度變化，及主要心血管事件（死亡、心肌梗塞、中風、及心血管介入治療）的發生率。此計劃執行至今已收入 140 位受試者，共有 110 位完成第二十四個月的 MDCT 檢查。本研究已登錄於臨床試驗網站(No. NCT00155012)。初步分析顯示使用胰島素增敏劑 pioglitazone 不只能夠使冠狀動脈鈣化的進展停止，三分之一的病患甚至呈現冠狀動脈鈣化程度減少的現象。我們亦將進入研究時所做之 MDCT 影像加以分析，發現心外脂肪層的厚度與代謝症候群有密切之關聯，且此關聯非與整體之心外脂肪層的量、而僅與存於左房室溝（left atrioventricular groove）中之心外脂肪層厚度有關。此發現乃世界首度，極具原創性。惟仍待更多研究驗證。本研究還有更多之相關分析在陸續進行中。

臨床意義：本研究將是第一個經由非侵入方式直接檢視冠狀動脈整體動脈硬化狀態、斑塊性質、甚至包括對心外膜脂肪層以評估胰島素增敏劑之療效之研究。此研究不僅將提供我們對動脈硬化塊脆弱性之演化過程的深入瞭解，也可以藉此建立評估整體冠狀動脈脆弱性的技術平台。

英文摘要:

Keywords: computed tomography, coronary artery disease, insulin resistance, insulin sensitizer, plaque

Background: Type 2 diabetes and its antecedent, metabolic syndrome are important risk factors for premature and accelerated atherosclerotic cardiovascular diseases. However, glycemic control by provision of endogenous or exogenous insulin induced only modest and not statistically significant reduction of the risk of myocardial infarction. We and other investigators have demonstrated that the use of insulin sensitizer, thiazolidinediones, resulted in favorable antiatherosclerotic effects in metabolic syndrome patients with or without overt type 2 diabetes. Vulnerable coronary plaques can be non-invasively detected by the high-resolution 16-slice/64-slice multi-detector computed tomography (MDCT). In this ongoing prospective, randomized, open-label 2-year study, we evaluated the efficacy of pharmacological therapy targeted to reduce insulin resistance on the progression and compositional change of non-obstructive coronary atherosclerotic plaques and epicardial fat by serial MDCT follow-up in patients with type 2 diabetes or non-diabetic metabolic syndrome during a 2-year period.

Methods and Results: Patients aged ≥18 years conformed to the diagnosis of type 2 diabetes or metabolic syndrome criteria in ATP III and with objective evidence of myocardial ischemia underwent MDCT coronary angiography and percutaneous coronary angiography and intervention if appropriate. Patients deemed eligible (with one or more ≥20% and <70% stenosis in at least one coronary artery) were then randomly assigned in a 1:1 ratio to receive pioglitazone (30 mg/d) or placebo in an open-label fashion. Patients with type 2 diabetes assigned to the placebo group were not allowed to be treated with any insulin sensitizer. The target for glycemic control in patients with type 2 diabetes in both groups is reduction of HbA_{1c} to ≤7.0%. A total of 120 patients are planned to be included, and the follow-up period is 2 years. To assess the progression of coronary atherosclerosis, MDCT coronary angiography/scanning were performed at baseline and 3, 6, 12, and 24 months of follow-up. Blood samples were also obtained at baseline and 3, 6, 12, and 24 months of follow-up for the measurement of various conventional and novel coronary risk factors. We obtained DNA specimen from blood drawn at baseline for genotyping. The primary end-points include changes from baseline in total plaque volume, plaque characteristics (as determined by CT-density values and other morphological features), and total coronary calcium score. The secondary end-points include percent change from baseline in calcium volume score in each coronary artery, changes in the amount of epicardial fat, percent change from baseline in plasma glucose/insulin homeostatic parameters and various risk markers, and the occurrence of a composite of major cardiovascular events (death from any cause, non-fatal myocardial infarction, stroke, and target vessel revascularization). The study was prospectively registered (number NCT00155012). We have completed the enrollment of 140 patients into the study. A total of 110 patients completed their 24-month follow-up MDCT examination. The preliminary result revealed that treatment with the insulin sensitizer, pioglitazone (30 mg/day), not only halted progression of coronary calcification, resulted in regression of coronary calcification in almost one-third participants. We also analyzed the amount of epicardial fat in the baseline MDCT and completed the statistical analysis regarding its relations with metabolic syndrome components and inflammatory markers. It is intriguing to note that only epicardial fat thickness in the left atrioventricular groove was correlated with all factors studied. Further analyses about the datasets will be ongoing.

Clinical Significance: This is the first human study to assess the antiatherosclerotic effects of insulin sensitizer by directly visualizing the atherosclerotic plaques of the whole coronary trees and the epicardial adipose tissue. It will provide us great insights regarding the evolution of coronary plaques and techniques of measuring the total vulnerability burden of the coronary arteries.

報告內容

研究計畫之背景及目的：

Type 2 diabetes and its antecedent, metabolic syndrome (insulin resistance syndrome), are important risk factors for premature and accelerated atherosclerotic cardiovascular diseases.[1,2] Normalization of all conventional risk factors does not eliminate the powerful association between diabetes/metabolic syndrome and coronary artery disease (CAD).[3] However, glycemic control by provision of endogenous or exogenous insulin targeted to lower median hemoglobin A1C to 7% over 10 years induced only modest and not statistically significant reduction of the risk of occurrence of myocardial infarction in the United Kingdom Perspective Diabetes Study (UKPDS).[4] One possible reason for the above-mentioned intriguing finding is that the hypoglycemic treatment (sulfonylurea or insulin) given in the UKPDS did not resolve the fundamental problem associated with diabetes, that is, insulin resistance.[5] With the advent of insulin-sensitizing pharmacological agents such as the thiazolidinediones that enhance insulin sensitivity in liver and muscle directly, therapy for diabetes has been directed toward amelioration of insulin resistance in addition to and as a means for achieving glycemic control. Several studies showed that the use of thiazolidinediones resulted in favorable effects on carotid intimal medial thickness and reduced intimal hyperplasia after coronary stenting in patients with diabetes.[6,7] The recently published PROactive study even demonstrated that treatment with pioglitazone significantly reduced the composite of all-cause mortality, non-fatal myocardial infarction, and stroke in high-risk type 2 diabetic patients.[8] We and other investigators further showed that thiazolidinediones ameliorated vascular inflammation and reversed endothelial dysfunction in pre-diabetic insulin-resistant subjects.[9,10]

Until relatively recently, the conventional wisdom has been that treatment of CAD should focus on relieving obstruction within epicardial arteries sufficient to induce myocardial ischemia under basal conditions or with physiological stress. Nevertheless, it has become increasingly clear that morbidity and mortality associated with CAD are often associated with lesions that are not obstructive until they rupture and precipitate clinical events. Such so-called vulnerable plaques are characterized by lipid-laden cores, thin fibrous caps, and a relative paucity of vascular smooth muscle cells.[11,12] Abluminal lesions are frequently found. Superficial vascular calcification is another morphological feature of vulnerable plaques.[12] Despite the correlation between vascular calcification and the degree of luminal narrowing is not significant, the amount of coronary calcification did correlate with the amount of total coronary atheroma volume.[13] Conventional coronary angiography is not suitable for identifying vulnerable plaques. They may be detected by intravascular ultrasound (IVUS) and recently developed high-resolution 16-slice/64-slice

multi-detector computed tomography (MDCT),[14,15] which we have accumulated experience with in identifying obstructive coronary atherosclerotic plaques and analyzing their composition with excellent accuracy.[16]

Rupture of vulnerable plaques is the proximate pathophysiological event most commonly responsible for acute coronary syndromes and their sequelae.[14] Attention may therefore be directed toward retarding or arresting abluminal coronary atherosclerosis, the evolution of vulnerable plaques, and factors precipitating plaque rupture. Unfortunately, it is not clear whether the progression of CAD and some implicated pathophysiological determinants regarding the evolution of vulnerable plaques, like coronary calcification, altered favorably with treatment targeted to reduce insulin resistance (thiazolidinediones) in patients with type 2 diabetes or metabolic syndrome.

In this ongoing prospective, randomized, open-label 2-year study, we evaluated the efficacy of pharmacological therapy targeted to reduce insulin resistance on the progression and compositional change of non-obstructive coronary atherosclerotic plaques in patients with type 2 diabetes or non-diabetic metabolic syndrome during a 2-year period. The first-year of the study was sponsored by grants from the National Science Council (NSC94-2314-B-002-292). We have completed the enrollment of 140 patients into the study. A total of 110 patients completed their 24-month follow-up MDCT examination. The preliminary result revealed that treatment with the insulin sensitizer, pioglitazone (30 mg/day), not only halt progression of coronary calcification, astonishingly resulted in regression of coronary calcification in almost one-third participants. The study was prospectively registered (number NCT00155012).

Details of the study has been described in the website, which can be accessed via http://www.clinicaltrials.gov. Briefly, for patients with type 2 diabetes, two treatment modalities are being tested: (1) pharmacological therapy designed to induce glycemic and metabolic control by provision of endogenous or exogenous insulin; and (2) pharmacological therapy designed to induce comparable glycemic and metabolic control by insulin sensitizer, namely, pioglitazone. The target for glycemic control in both groups is reduction of HbA_{1c} to $\leq$7.0%. For patients with non-diabetic metabolic syndrome, two treatment modalities compared are optimal medical therapy to normalize all conventional coronary risk factors and optimal medical therapy plus insulin sensitizer. The imaging modalities used to assess coronary plaques are both intravascular ultrasound (at baseline and 6 months of follow-up, if possible) and 16-slice MDCT (at baseline and 3, 6, 12, and 24 months after beginning of the study). The primary end-points include changes from baseline in total plaque volume, plaque characteristics (as determined by CT-density values and other morphological features), and total coronary calcium score. We will also analyze the relationships between baseline values and changes of various conventional as well as novel coronary risk factors (for example, sCD40 ligand, resistin, endothelin-1) and the antiatherosclerotic effect of the study drug (if there is). Moreover, the relationships between the polymorphism status of various candidate genes (for example, PPARγ) and the antiatherosclerotic effect of the study drug will also be explored. Because of the significant effects of pioglitazone on coronary calcification, we will also evaluate its effects on circulating markers of vascular

calcification, like Fetuin A, matrix gla protein, etc.[17]

研究方法：

Subjects and Study Design

Patients will be recruited from the Clinics at the National Taiwan University Hospital, without restriction to sex or socioeconomic status. Inclusion criteria are: (1) Age ≥18 years and the presence of type 2 diabetes mellitus or metabolic syndrome, not currently treated by thiazolidinediones. Diagnosis of metabolic syndrome is determined by criteria defined by the National Cholesterol Education Program Adult Treatment Panel III,[18] modified to use WHO proposed waist circumference cut-points for Asians.[10] Therefore, this requires subjects to have three or more of the following criteria: (i) waist circumference of >90 cm in men and >80 cm in women; (ii) serum triglycerides of ≥150 mg/dl; (iii) HDL-C levels of <40 mg/dl in men and <50 mg/dl in women; (iv) impaired fasting glucose of 110 to 125 mg/dl; or (v) blood pressure of ≥130/85 mmHg or treated hypertension; (2) Patients with objective documentation of myocardial ischemia undergoing percutaneous coronary angiography and the coronary arteriogram showing one or more ≥20% and <70% stenosis, which will be left untreated at physician's discretion, in at least one coronary artery; (3) The baseline MDCT coronary angiogram revealing one or more discernible plaque(s) untreated by stenting in at least one coronary artery; (4) Ability to perform all tasks related to glycemic control and risk factor management; (5) Written informed consent signed.

Major exclusion criteria are: (1) Class III or IV heart failure; (2) Creatinine >2.0 mg/dl; (3) Hepatic disease (ALT >3 times the upper limit of normal); (4) Poorly controlled diabetes mellitus (HbA_{1c} >13%); (5) Fasting triglycerides >1000 mg/dl in the presence of moderate glycemic control (HbA_{1c} <9.0%); (6) Non-cardiac illness expected to limit survival to less than two years; (7) Current alcohol or drug abuse; (8) Chronic steroid use judged to interfere with the control of diabetes, exceeding 10 mg; (9) Unable to understand or cooperate with protocol requirements.

Before enrollment into the study, all patients will undergo MDCT coronary angiographic examination and percutaneous coronary angiography and intervention if appropriate. After the completion of coronary angiographic study, patients deemed eligible will be randomly assigned in a 1:1 ratio to receive pioglitazone (30 mg/d) or placebo in an open-label fashion. Patients with type 2 diabetes assigned to the placebo group are not allowed to be treated with any insulin sensitizer. The target for glycemic control in patients with type 2 diabetes in both groups is reduction of HbA_{1c} to ≤7.0%. All patients will be instructed to adhere to the American Heart Association Step 1 diet throughout the study and receive standard medical therapy, including aspirin, lipid-lowering therapy, with or without clopidogrel. A total of 120 patients are planned to be included, and the follow-up period is 2 years.

To assess the progression of coronary atherosclerosis, MDCT coronary angiography/scanning will be performed at baseline and 3, 6, 12, and 24 months of follow-up. Follow-up coronary angiography and intravascular ultrasound study will be performed at 6 months if patients agree. Blood samples will also be obtained at baseline and 3, 6, 12, and 24

months of follow-up for the measurement of various conventional and novel coronary risk factors and other components that are part of the safety assessment. We also obtain DNA specimen from blood drawn at baseline for genotyping.

The primary end-points include changes from baseline in total plaque volume, plaque characteristics (as determined by CT-density values and other morphological features), and total coronary calcium score. The doctors analyzed the MDCT results are blinded to the medications studied. The secondary end-points include percent change from baseline in calcium volume score in each coronary artery, percent change from baseline in plasma glucose/insulin homeostatic parameters and various risk markers, and the occurrence of a composite of major cardiovascular events (death from any cause, non-fatal myocardial infarction, stroke, and target vessel revascularization).

Multidetector Computed Tomography Analysis

A 16/64-slice MDCT (Lightspeed16, GE healthcare, Milwaukee, USA) scan is performed with 100 ml of nonionic contrast agent and electrocardiographically triggered slice acquisitions. All patients will receive -blocker therapy to decrease heart rate (<65 beats/min) and improve image quality. Rotation time is 420 ms, and total breath-hold is about 20 seconds. Diastolic gating and 3-dimensional reconstruction are performed at 60% RR intervals. The evaluation of the MDCT angiograms is performed by 2 experienced investigators, who are unaware of the clinical history of the patients. In case of nonconsensus between the readers, a joint reading will be performed and a consensus will be reached.

Coronary plaques are defined as structure >1mm^2 within the coronary artery whose density differed from that of the contrast-enhanced vessel lumen (Figures 2 & 3). Plaques are divided into calcified (density >130 Hounsfield U [HU] in native scans), non-calcified, or mixed lesions. Calcified lesions with an area <5 mm^2 are defined as spotty. Calcified lesions with a plaque area >5 mm^2 are classified as heavily calcified. Non-calcified lesions are identified on the basis of their lower density compared with the contrast-enhanced vessel lumen (density <130 HU).[19] Lesions are defined as mixed if the plaque area consisted of >50% of noncalcified plaque tissue. This ratio for the definition of mixed plaque is chosen because calcium causes blooming artifacts due to partial volume effects that occur in the immediate neighborhood of calcium and may be confused with small areas of noncalcified tissue.[13] The total number of plaques is counted. Maximal and minimal plaque thicknesses are measured and eccentricity index is then calculated. For the calculation of the plaque area, we use sliding thin slab maximum intensity projections, and all plaques are measured in the longitudinal vessel direction (Figure 4). The density of each plaque is determined by measuring the density in ≥16 randomly selected points with the plaque area.[17] Homogenous plaque is defined as <30% density difference between the highest and lowest regions of interest density. Furthermore, the volumetric calcium score is determined in non-enhanced scans using a fully automatic software package (Advantage Workstation, GE healthcare, Milwaukee, USA).

Intraplaque hypodensity is considered present if a 30% decrease in HU is individualized in

plaque compared with the mean value of the other regions of interest, excluding bright echoes corresponding to calcifications. Plaque disruption is considered present if infiltration of contrast medium or an excavation is seen in the plaque. This infiltration is carefully checked to differentiate if from a collateral branch origin or intraplaque calcification. Positive remodeling is visually assessed on longitudinal reconstruction.

Laboratory Assays

Venous blood samples are placed into tubes containing EDTA. Samples are centrifuged within 30 minutes at 2000 rpm for 10 minutes. The plasma will then be separated and stored at -70℃ until analysis. Levels of total cholesterol, total triglycerides, LDL-C and HDL-C are assayed by routine laboratory techniques with the use of methodology of the Lipid Research Clinics, as reported previously. If plasma triglycerides are ≥400 mg/dL, LDL-C will be assessed by a direct method. Plasma concentrations of interleukin (IL)-1 ，IL-6, CD40, sCD40L, endothelin-1, adiponectin, resistin, fetuin A, and matrix gla protein are determined in duplicate using commercially available immunosorbent kits (IL-1 ，and IL-6, R&D Systems; CD40 and sCD40L, Bender MedSystems). High-sensitivity CRP will be assayed by rate nephelometry (Dade Behring, Newark, Del.). High-sensitivity CRP will be assayed by rate nephelometry (Dade Behring, Newark, Del.). Insulin concentration is determined in duplicate using a commercially available immunosorbent kit (Immuno-Biological Laboratories, Hamburg, Germany). Dilution curves of the plasma samples are parallel to those of the standard. The marker of insulin resistance, homeostasis model assessment estimate of insulin resistance (HOMA-IR),[10] is defined as follows: fasting plasma insulin (μU/ml) × fasting glucose (mmol/l)/22.5. Routine chemical clinical analyses will be performed by standard methods subjects to strict quality control. The coefficients of variation are <5% for every type of measurement.

Statistical Analysis

The data are analyzed by nonparametric methods to avoid assumptions about the distribution of measured variables. Comparisons between groups are made using the Mann-Whitney U test. The differences between baseline and post-treatment values are analyzed using the Wilcoxon signed-rank test. Mann-Whitney analysis is used for comparison of the percentage changes between baseline and post-treatment values in patients receiving pioglitazone versus those receiving placebo. The association of these measurements with other baseline biochemical parameters is assessed by the Spearman rank correlation test. Multivariate regression analysis is performed to test the independent association between changes in coronary atherosclerosis and various risk factors as well as genotypes. Statistical significance is set at $P < 0.05$.

結果與討論：

In this ongoing prospective, randomized, open-label 2-year study, we evaluated the efficacy of pharmacological therapy targeted to reduce insulin resistance on the progression and compositional change of non-obstructive coronary atherosclerotic plaques and the amount of

epicardial fat in patients with type 2 diabetes or non-diabetic metabolic syndrome during a 2-year period. We have completed the enrollment of 140 patients into the study. A total of 110 patients completed their 24-month follow-up MDCT examination. The preliminary result revealed that treatment with the insulin sensitizer, pioglitazone (30 mg/day), not only halted progression of coronary calcification, resulted in regression of coronary calcification in almost one-third participants. We also analyzed the amount of epicardial fat in the baseline MDCT and completed the statistical analysis regarding its relations with metabolic syndrome components and inflammatory markers (**Table and Figure**). We have for the first time demonstrated that only epicardial fat thickness in the left atrioventricular groove, rather than the averaged thickness or areas, was correlated with all factors studied. Further analyses about the datasets will be ongoing.

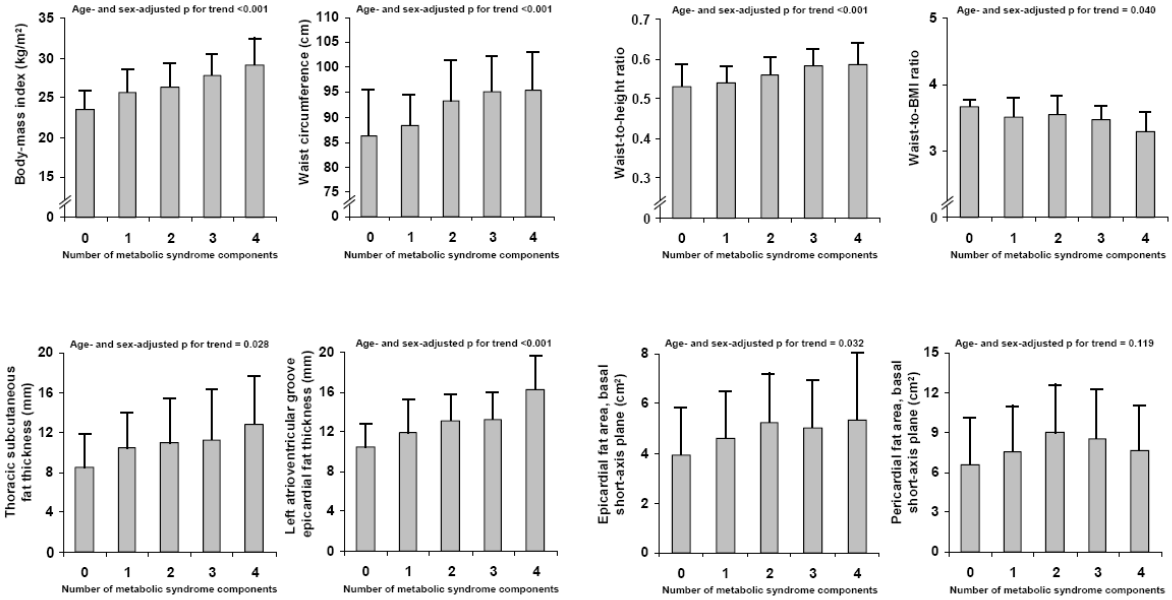

Table 8. Values of Adipose Tissue and Anthropometric Measurements in Relation to the Number of Metabolic Syndrome Components

	3 metabolic syndrome components	4 metabolic syndrome components
BMI	0.320‡	0.395‡
Waist circumference	0.306‡	0.359‡
Waist-to-height ratio	0.309‡	0.350‡
Waist-to-BMI ratio	-0.253‡	-0.224*
Thoracic subcutaneous fat thickness	0.140	0.217*
Epicardial fat thickness		
Left AV groove	0.397‡	0.404‡
Right AV groove	0.115	0.083
Anterior IV groove	0.004	0.031
Superior IV groove	0.113	0.090
Inferior IV groove	-0.054	-0.091
Mean	0.175*	0.161
Epicardial fat area		
Four-chamber plane	0.133	0.093
Basal short-axis plane	0.203*	0.218*
Mid-ventricular short-axis plane	0.142	0.144
Apical short-axis plane	0.169*	0.177*
Mean short-axis plane	0.182*	0.191*
Pericardial fat area		
Four-chamber plane	0.148	0.160
Basal short-axis plane	0.172*	0.170*
Mid-ventricular short-axis plane	0.107	0.096
Apical short-axis plane	0.118	0.127
Mean short-axis plane	0.169*	0.167*

*p < 0.05; †p < 0.01; ‡p < 0.001.

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