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厚生労働科学研究費補助金

循環器疾患等総合研究事業

各種高脂血症治療薬の糖尿病性心血管病進展予防効果の総合的検討に関する研究
（臨床研究実施チームの整備）

平成16年度　総括・分担研究報告書

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平成17（2005）年３月

目　　次

I. 総括研究報告

厚生科学研究費補助金（循環器疾患等総合研究事業）総括研究報告書

各種高脂血症治療薬の糖尿病性心血管病進展予防効果の総合的検討（臨床研究実施チームの整備）

（主任）研究者　井口　昭久　名古屋大学医学部附属病院病院長、名古屋大学大学院医学系研究科老年科学、

研究要旨　高齢者糖尿病患者の血清脂質管理の実態を、高脂血治療薬投与及び動脈硬化学会ガイドライン準拠率を中心に検討した。

目的）高齢者における糖尿病合併高脂血症罹患者に対する薬物治療の実態を検討した。高脂血治療薬投与及び動脈硬化学会ガイドライン準拠率を中心に検討した。

虚弱及び自立高齢者に分類し高脂血症と各種バイオマーカーの関係を検討した。

結果）1670名の高齢者のうち、高脂血症の罹患者は44%で内訳は、998名の自立高齢者には約51%、672名の虚弱高齢者には34%の高脂血症合併を認めた。高脂血症ガイドライン脂質管理値達成率は58%、69%であった。糖尿病合併者（12%）の高脂血症の頻度は、各々約12%、6%と前者は糖尿病合併者の80%に認めたが脂質管理目標値達成率は29%, 52%であった。

A. 採択された研究事業での研究概要

本邦においては糖尿病罹患者が増加しており,高脂血症合併例の増加及び心血管合併症のリスクとしての大きさが注目されている。加齢そのものによっても高脂血症患者の頻度は増大する。糖尿病性心血管病変は耐糖能異常の段階から進行し,長期罹患者が増加している。糖尿病患者の死因としては心血管合併症によるものが最も多く予防法確立が急務である。一方、糖尿病合併高脂血症の治療効果は血糖降下療法を凌駕する可能性も欧米の大規模臨床試験で報告され、日本動脈硬化が学会は糖尿病罹患者は血清LDL-Cholesterolの管理目標値をB３以上 120　mg/dl以下としている。さらに米国では100mg/dl以下と推奨している。本研究は代謝内分泌学,循環器学,老年学,臨床薬理学医により研究班を結成し、エビデンスに基づく高脂血症合併糖尿病心血管病予防指針策定を目標とする。

B. 採択された研究事業での研究実績

当該施設では糖尿病,耐糖能異常,非糖尿病,210,36,106名を登録し追跡調査を開始した。登録者平均年齢は64.5歳,各群の高脂血症合併率は78.2、72.2、53.5%であった。結果は、糖尿病コントロール指標値HbA1C 7.09%、TC 206.3,TG144.1,HDL-C 55.5mg/dlであった。糖尿病＋高脂血症群は脂質管理目標達成率32.2%と低く、虚血性心血管病の発症入院、インターベンション等を評価する。脂質管理目標値達成によるイベント予防効果,高脂血症病態による発症頻度の差異、脳血管障害に対する効果，医療経済効果に方向性を出す事を目指す。当該施設の個別研究として凝固系等の遺伝子素因を評価いている。治療目標を米国推奨厳格基準群と本邦ガイドライン準拠群での無作為二重盲検を先行するため倫理委員会の承認を得た。非侵襲的検査—運動負荷試験,頸動脈超音波,内皮機能とバイオマーカーより総合判定する。心不全,認知症を二次エンドポイントとし解析する。

（倫理面への配慮）

研究対象者に対してインフォームドコンセントを徹底し、協力者の利益が損なわれる事がないように十分に留意する。本研究は名古屋大学医学部附属病院倫理委員会承認後に施行されている。血管内皮機能検査は非侵襲的検査のみ行っている。プライバシーは匿名化を行い個人名が特定化されないよう細心の注意をはかっている。

C. 考察

本研究の意義は具体的な糖尿病、高脂血症の治療指針の策定にあるが、更に、長寿社会,日本で増加する生活習慣病自体の合併、心及び脳血管障害合併者の診療、二次予防は、総合診療学、老年科学の領域でも重要と考えられる。

D. 健康危険情報

現在のところは認めない。

E. その他実施した臨床研究・治験の概要及び実績

厚労省長寿科学総合研究事業『高齢者糖尿病治療と健康寿命に関するランダム化比較研究』(６例,100%)

厚労省長寿委託研究事業『高齢女性に対するホルモン補充療法に関する総合的研究』（4２例.88%）

EPA の心血管事故発症に及ぼす影響の大規模臨床試験(JLIS)（3名,100%）

臨床研究実施チームの組織

（1） 臨床研究実施チーム（a組）

	①若手医師及び臨床研究協力者に対する指導者	②若手医師	③臨床研究協力者
氏　　　　名	林　登志雄	大澤　雅子	平井　寿子
分担する研究項目	診療,同意取得、検査,群分け処方	診療,同意取得検査,データ解析	検査、データ解析
最終卒業学校・卒業年次・学位及び専攻科目	信州大学医学部医学科昭和 59 年卒・医学博士・老年科学	岐阜大学医学部医学科平成 10 年卒・医学士・老年科学	岐阜大学農学部生命科学科修士平成 10 年卒・農学修士・老年科学

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The treadmill exercise-tolerance test is useful for the prediction and prevention of ischemic coronary events in elderly diabetics

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Abstract

Background: Approximately 80% of cases of ischemic heart disease (IHD) occur in patients with nonstenotic coronary arteries, and few studies have systematically assessed exercise testing (TMT) as a predictor of risk in the elderly. **Methods:** TMT was carried out using a protocol for the independent and active elderly (n=176). After 4.1±0.5 years follow-up, logistic regression analysis was performed for each coronary risk factor such as diabetes mellitus (DM) and hypercholesterolemia (HC). According to the results, patients were divided into Gp HC, hypercholesterolemic patients; Gp DM, diabetics; Gp HC+DM, hypercholesterolemic diabetics; and Gp C, nonhyperlipidemic and nondiabetics. Sensitivity and specificity of TMT for IHD (significant stenosis or acute coronary syndrome) were analyzed. **Results:** Odds ratios for each risk factors are as follows: DM, 4.167; HC, 4.485; and DM+HC, 8.652. Notably, TMT was 17.59. Age was a significant risk, but hypertension was not. Positive ischemic signs in TMT were observed in 52.7%, 28.6%, 33.3%, and 16.3% in the Gp HC+DM, HC, DM, and C groups, respectively. Only three participants complained of chest pain during the TMT. Significant stenosis was observed in 75.0%, 71.4%, 69.2%, and 60.0% of coronary angiography (CAG)-receiving patients of Gp HC, DM, HC+DM, and C. During the observation term, acute coronary syndromes occurred in 4.7%, 3.3%, 5.5%, and 0% of patients in the Gp HC, DM, HC+DM, and C groups, respectively. The sensitivity of TMT for IHD was higher than 66.7% and specificity was higher than 94.1% in each group. **Conclusion:** An exercise tolerance test in the elderly, especially for diabetics and hypercholesterolemic patients, is useful for the diagnosis of IHD.

1. Introduction

Recent mega-trials have revealed that strict control of complicated coronary risk factors such as hyperlipidemia is important for the prevention of diabetic vascular lesions (Jonsson, Cook, & Pedersen, 1999). Exercise stress testing is an accepted means of estimating and diagnosing cardiovascular disease, as well as of predicting cardiovascular and all-cause mortality (Gianrossi, Detrano, Mulvihill, et al., 1989). However, approximately 80% of cases of ischemic heart disease (IHD) occur in patients with nonstenotic coronary arteries, and these cases cannot be predicted by an exercise-tolerance test (Bezerra, Higuchi, Libby, Ramires, et al., 2001). Furthermore, few studies have systematically assessed exercise testing as a predictor of risk in the elderly. Diabetic coronary lesions are known to have long segmental narrowing, and the incidence of IHD seems to be especially increased in patients who have had diabetes for more than 10 years (Al-Attar, Mahussain, & Sadanandan, 2002; Stein, Weintraub, Gebhart, et al., 1995). We have speculated that an exercise-tolerance test would be useful for the evaluation and prevention of IHD in elderly diabetics, if it could be carried out in a safe manner. We therefore modified the protocol of the exercise burden for the treadmill exercise-tolerance test (TMT) to make it more suitable for elderly patients.

The present study focused on the relationship between the frequency of cardiovascular ischemia, the exercise-tolerance test, and coronary risk factors in the elderly.

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2. Research design and method

2.1. Patient selection

Between April 1997 and March 2000, 342 patients were enrolled in this study. All patients were ambulatory and were either referred to our geriatric clinic (Nagoya University Hospital) or enrolled in our hospital to receive educational hospitalization for diabetes. Among them, 176 patients who were older than 65 years and who underwent an exercise-tolerance treadmill test were prospectively enrolled and followed for 4.1±0.5 years (Table 1). All patients gave their informed consent to participate in this study. None of the patients had experienced a myocardial infarction in the 3 months prior to enrollment, and they were independently active in daily life, as determined by their Lawton and Berthal scores (Collin, Wade, Davies, & Horne, 1988; Lawton & Brody, 1969).

2.2. Protocol and method

TMT was performed according to a protocol for the elderly, which we adapted from a protocol used for veterans in the United States (Prakash, Myers, & Froelicher, 2001). We changed the test so that each step lasted 2 min due to the age-related limitation of exercise tolerance (Hagberg, 1994; Tamesis et al., 1993; Table 2). The chronotropic response to exercise was assessed by estimating the proportion of the heart-rate reserve (220-age) used at peak exercise (Lauer, Francis, Okin, et al., 1999). Ischemic changes in the treadmill test were diagnosed using the Minnesota protocol; in brief, 1.0 mm or more ST segment elevation or depression in two or more leads was identified as positive. Exercise tolerance was estimated as METS, which was calculated from the participant's TMT results, body weight, age, and estimated Vo2 at rest. Plasma lipid and glucose levels were also measured. The diagnosis of hypercholesterolemia (HC) and diabetes followed the guidelines of the American Heart Association and Diabetes Association (Krauss, Eckel, Howard, et al., 2000; Resnick, Harris, Brock, et al., 2000). This study was approved by our institutional review board.

2.3. Follow-up data/definition of adverse outcome

All patients were followed until April 2002, with the mean follow-up period being 4.1±0.5 years after the treadmill test. The outcome was determined from patient interviews, hospital chart reviews, and telephone interviews. An adverse outcome was defined as the finding of significant stenosis in coronary angiography (CAG) with or without coronary intervention, such as percutaneous coronary angioplasty or ischemic cardiac events in the follow-up term. Cardiac events were defined as cardiac death, nonfatal MI, and resuscitated ventricular fibrillation or tachycardia after the TMT. Only the most severe outcome was considered an endpoint. Twenty-nine patients were excluded because of patient or physician refusal to follow-up (n=13), an inability to repeat the exercise treadmill test safely due to hearing loss (n=2), or geographic relocation (n=14). A total of 147 elderly individuals could be followed, and data on their histories of ischemic coronary disease, results of CAG, medication, and other parameters were recorded (Table 1). Based on the odds ratios evaluated as described below, patients older than 65 years were divided into four groups: Gp HC, hypercholesterolemic patients (n=42); Gp diabetes mellitus (DM), diabetic patients (n=30); Gp HC+DM, hypercholesterolemic and diabetic patients (n=36); and Gp C, nondiabetic and nonhyperlipidemic patients (n=39).

Table 1
Profile of patients

Patients number	147 (Male 71, Female 76)
Age (years)	71.7+0.4
Hypercholesterolemia	78 (Male 38, Female 40)
Diabetes mellitus (DM)	66 (Male 32, Female 34)
Hypertension	78 (Male 40, Female 38)
[Hypercholesterolemia+DM]	[36 (Male 17, Female 19)]

Table 2
Protocol of treadmill test for elderly

Stage	1	2	3	4	5	6	7	8	9
Period (min)	2	2	2	2	2	2	2	2	2
Speed (miles/h)	1	2	2	2	2	2	2.5	3.3	3.3
Gradient (%)	0	0	5	10	15	20	20	20	25
METs	2.5	3	5	6	8	9	10	11	13

2.4. Statistical analysis

Continuous data were expressed as the means±S.D. Categorical variables were analyzed by the chi-square test or Fisher's Exact Test. Continuous variables within groups were analyzed by repeated measures using analysis of variance (ANOVA). The Student's t test was used to identify significant differences in means. Stepwise multiple logistic regression analyses were used to identify the independent predictors of outcome, as well as the additive prognostic values of the clinical data and the exercise treadmill test. Fisher's Exact Test was used to calculate odds ratios or the probability of detecting any variables included in the logistic regression analysis in patients with adverse outcomes relative to patients with good outcomes.

3. Results

The odds ratios of each risk factor as determined by logistic regression analysis are shown in Table 2. Briefly, the odds ratios were as follows: DM, 4.167; HC, 4.485; and DM+HC, 8.652 (P<.01, respectively). That of age was significantly high (2.953; P<.05), whereas that of hypertension was not significant (2.151; P=.053). Notably, the odds ratio for positive ischemic signs as evaluated by TMT was 17.59.

Table 3
Odds ratio and 95% CI of each risk factor by logistic regression analysis

Hypercholesterolemia	4.485* (1.495–12.28)
DM	4.167* (1.477–10.81)
DM+Hypercholesterolemia	8.652* (2.543–13.68)
Hypertension	2.151 (0.845–9.26)
Age	2.953** (0.985–10.36)
Positive finding in TMTest	17.590*** (6.77–47.02)

* $P<.01$.
** $P<.05$.
*** $P<.001$.

We therefore divided the patients into four groups (Table 3): Gp HC, hypercholesterolemic patients (n=42; 72.0±0.5 years old; LDL-C, 150.7±10.4 mg/dl; exercise tolerance, 6.4±0.2 METs); Gp DM, diabetic patients (n=30; 72.3±0.9 years old; HbA1C, 7.6±0.5 g/dl; disease duration, 12.0±1.2 years; 6.0±0.5 METs); Gp HC+DM, hypercholesterolemic and diabetic patients (n=36; 71.4±0.8 years old; LDL-C, 149.5±11.5 mg/dl; HbA1C, 7.0±0.3 g/dl; disease duration for diabetes, 12.9±1.1 years; 6.4±0.3 METs); and Gp C, nondiabetic and nonhypercholesterolemic patients (n=39; 71.6±0.9 years old; 6.2±0.4 METs). The mean age and the frequency of other coronary risk factor complications, such as hypertension, smoking, and others, were not significantly different among the four groups. The TMT-positive ratios were 28.6%, 33.3%, 52.7%, and 16.3% in participants from the Gp HC, DM, HC+DM, and C groups, respectively (Fig. 1). Only three participants complained of chest pain during the TMT test (two in Gp HC+DM and one in Gp HC), and all of them became symptom-free within 5 min after exercise; all other positive patients were symptom-free. The ratios of patients receiving CAG per TMT-positive patient within 8 months after TMT were 66.7%, 63.6%, 68.4%, and 62.5% in the Gp HC, DM, HC+DM and C groups, respectively. CAG was not done for the following reasons: (1) patient refusal, lack of understanding of the CAG, and/or coronary intervention due to risk (n=11); (2) a high risk of coronary intervention for other general diseases such as chronic renal failure or cerebral infarction (n=6); and (3) physician refusal due to the risk of coronary intervention or CAG because of cognitive impairment, and others (n=6). In some patients who did not receive CAG but were suspected to have stenotic lesion by other examinations, medication such as anti-platelets and/or NO donors, such as isosorbide dinitrate, was prescribed. More than 75% stenosis was observed in 75.0%, 71.4%, 69.2%, and 60.0% of CAG-receiving patients of the Gp HC, DM, HC+DM, and C groups, respectively, and coronary intervention was performed in all of these cases (Fig. 1). During the 4.1±0.5 years of observation, ischemic coronary diseases such as angina pectoris or acute myocardial infarction occurred in 4.7% (8.3), 3.3% (10.0), 5.5% (5.3), and 0% of patients in the Gp HC, DM, HC+DM, and C groups, respectively (the percentage for TMT-positive patients). Older patients (older than 75 years of age) had more events (7.3% vs. 0%) than did the relatively younger patients (65–74 years; $P<.001$). Cardiac death was significantly more frequent in older

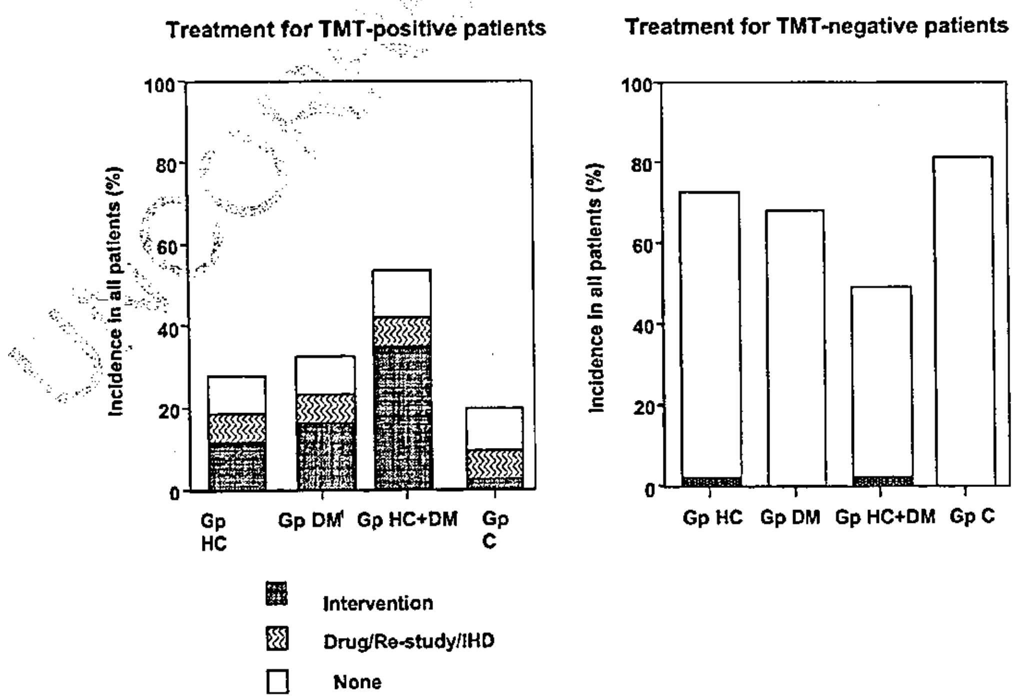

Fig. 1. Left: The frequency of TMT-positive findings and the corresponding treatments chosen for each disease group. Gp HC: hyper-cholesterolemic patients (n=42); Gp DM: diabetic patients (n=30); Gp HC+DM: hypercholesterolemic and diabetic patients (n=36); Gp C: nondiabetic and nonhypercholesterolemic patients (n=39). Right: The frequency of TMT-negative findings and the corresponding treatments chosen for each disease group.

Table 4
Patients profile who have coronary stenosis by CAG study, acute coronary syndrome, or drug treatment without CAG

	Percentage (%) of possible IHD				
	Total	In TMT-positive patients	In TMT-negative patients	Sensitivity of TMT for IHD	Specificity of TMT for IHD
Gp HC (42)	23.2	75.0	5.6	72.7≦	96.7
Gp DM (30)	26.7	72.7	0	66.7≦	100
Gp HC+DM (36)	41.7	73.7	5.9	68.8≦	94.1
Gp C (39)	10.3	66.7	0	66.7≦	100

Possible IHD means significant stenosis, ACS, and drug treatment during the observation term (4.1±0.5 years).
Sensitivity is calculated by (ACS and significant stenosis)/(TMT-positive patients−patients treated by drug without CAG).
Specificity is calculated by (no ACS or no significant stenosis)/(TMT-negative patients).

patients (P<.001). Finally, significant stenosis observed by CAG, IHD, or medical intervention during follow-up term was observed in 75.0%, 72.7%, 73.7%, and 66.7% of TMT-positive patients in the Gp HC, DM, HC+DM, and C groups, respectively. Sensitivity and specificity were calculated as shown in Table 4, and they mean the reliability and usefulness of TMT for the diagnosis or speculation of IHD.

4. Discussion

The elderly population is increasing all over the world, and Japan is now the world's most aged society. Elderly individuals with IHD have higher rates of physical disability, as defined by a diminished ability to perform the activities of daily living, than do persons without IHD. Older age and clinical manifestations of angina pectoris or chronic heart failure are known to be associated with the highest rates of disability (Morey, Pieper, Crowley, Sullivan, & Puglisi, 2002). The odds ratio for age was also found to be significantly high in the present study (2.953; P<.05).

TMT using a protocol for the elderly was shown in the present study to be safe and possibly useful for maintaining independent activities of daily living in the elderly, as the positive ischemic signs evaluated by TMT showed an odds ratio of 17.59 despite the fact that 90% of patients testing positive were asymptomatic. The exercise tolerance (mean=6.1±0.5 METs) determined in the present study indicates that the elderly have the capacity to maintain the activities of daily living, including voidance and using the stairs. The optimal test duration is from 8 to 12 min, and the protocol workloads should be adjusted to permit this duration (Myers & Froelicher, 1993).

The odds ratios for each risk factor, as determined by logistic regression analysis, were the following: DM, 4.167; HC, 4.485; and DM+HC, 8.652 (P<.01, respectively). Hypertension, however, was not found to be significant (2.151; P=.053). Although the importance of diabetes as a coronary risk factor is well known, almost all patients with a positive TMT test were asymptomatic and showed a relatively high percentage of coronary stenosis. TMT is useful in screening for diabetic coronary macroangiopathy. The frequency of the TMT-positive ratio was found to be relatively high in the present study; we speculate that this finding was due to the fact that the study participants had suffered from diabetes for long periods and to our adoption of the standards of the AHA exercise-tolerance test (Gibbons, Balady, Basley, et al., 1997). We also examined 166 patients younger than 65 years as young control participants; these patients underwent TMT using a symptom-limited modified Bruce protocol and were followed for 4.0±0.8 years (data not shown). Their positive ratios were less than 15%, even in the patients with diabetes complicated with hyperlipidemia (data not shown). Despite a paucity of data on the predictive value of stress tests in older populations, current stress-testing guidelines extend the following recommendations to all adults aged 65 and older (Gibbons et al., 1997). The value of exercise training in patients older than 65 years is supported by a recent study involving 772 men with coronary heart disease, in which physical activity (walking, in particular) for a total of at least 4 hours per week was associated with a significant reduction in overall mortality. Thus, TMT should be useful in cardiac-rehabilitation programs for the elderly. Regarding the interpretation of these findings, a number of limitations should be mentioned. Goyara, Jacobsen, Pellikka, et al. (2000) found that exercise capacity, but not ST-segment changes, was predictive of mortality and cardiovascular events, but they did not distinguish patients who were older than 75 years of age from those who were younger. These findings do not agree with those of the present study, although we cannot identify the reason for this discrepancy. In our study, some patients did not undergo CAG due to patient or physician refusal, and others. Although the risk associated with CAG is small, some physicians cannot justify it fully to patients. This study was also confined to those patients who were referred for exercise testing and thus were able to walk on a treadmill. Despite these facts, our results demonstrated conclusively that TMT was useful for the prevention and management of ischemic coronary artery disease in elderly patients, especially in those with diabetes.

Especially, the high value of specificity of TMT means that TMT-negative finding means the less possibility of IHD and that TMT can be used as screening test of IHD for independent elderly.

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