表1 サンプルサイズ(P_0=0.01、RR=2、α=0.05(両側)、β=0.2)

	K (非曝露/曝露)	m	非曝露群	曝露群	サブコホート	ケース	詳細調査	全コホート
コホート	0.5	-	1810	3620	-	91	5430	5430
	1	-	2319	2319	-	70	4638	4638
	2	-	3317	1659	-	66	4976	4976
ケース・コホート	0.5	0.5	5430	10860	136	272	406	16290
	1	0.5	6957	6957	105	209	312	13914
	2	0.5	9951	4977	100	199	298	14928
	0.5	1	3620	7240	181	181	359	10860
	1	1	4638	4638	139	139	276	9276
	2	1	6634	3318	133	133	264	9952
	0.5	2	2715	5430	272	136	403	8145
	1	2	3479	3479	208	104	309	6958
	2	2	4976	2489	200	100	297	7465
	0.5	5	2172	4344	545	109	645	6516
	1	5	2783	2783	415	83	492	5566
	2	5	3981	1991	400	80	475	5972
	0.5	10	1991	3982	1000	100	1083	5973
	1	10	2551	2551	770	77	835	5102
	2	10	3649	1825	730	73	793	5474

表2 Power(P_0=0.01、RR=2、α=0.05(両側))

	K (非曝露/曝露)	全コホート	m	非曝露群	曝露群	サブコホート	ケース	Power
コホート	0.5	5000	-	3333	1667	-	67	0.764
	1	5000	-	2500	2500	-	75	0.829
	2	5000	-	1667	3333	-	83	0.802
ケース・コホート	0.5	15000	0.5	10000	5000	100	200	0.764
	1	15000	0.5	7500	7500	113	225	0.829
	2	15000	0.5	5000	10000	125	250	0.802
	0.5	10000	1	6667	3333	133	133	0.764
	1	10000	1	5000	5000	150	150	0.829
	2	10000	1	3333	6667	167	167	0.802
	0.5	7500	2	5000	2500	200	100	0.764
	1	7500	2	3750	3750	226	113	0.829
	2	7500	2	2500	5000	250	125	0.802
	0.5	6000	5	4000	2000	400	80	0.764
	1	6000	5	3000	3000	450	90	0.829
	2	6000	5	2000	4000	500	100	0.802
	0.5	5500	10	3667	1833	730	73	0.764
	1	5500	10	2750	2750	830	83	0.829
	2	5500	10	1833	3667	920	92	0.802

表3 複数イベントとサンプルサイズ(P_D=0.01、RR=2、α=0.05(両側)、β=0.2、r=2

	K (非曝露/曝露)	m	非曝露群	曝露群	サブコホート	ケース	その他のケース	詳細調査	全コホート
コホート	0.5	-	6074	3037	-	91	2187	9111	9111
	1	-	3496	3496	-	70	1678	6992	6992
	2	-	2220	4440	-	67	1598	6660	6660
ケース・コホート	0.5	0.5	18222	9111	137	273	6560	6970	27333
	1	0.5	10488	10488	105	210	5034	5349	20976
	2	0.5	6660	13320	100	200	4795	5095	19980
	0.5	1	12148	6074	182	182	4373	4737	18222
	1	1	6992	6992	140	140	3356	3636	13984
	2	1	4440	8880	133	133	3197	3463	13320
	0.5	2	9111	4556	274	137	3280	3691	13667
	1	2	5244	5244	210	105	2517	2832	10488
	2	2	3330	6660	200	100	2398	2698	9990
	0.5	5	7289	3645	545	109	2624	3278	10934
	1	5	4196	4196	420	84	2014	2518	8392
	2	5	2775	5328	405	81	1945	2431	8103
	0.5	10	6682	3341	1000	100	2406	3506	10023
	1	10	3846	3846	770	77	1846	2693	7692
	2	10	2442	4884	730	73	1758	2561	7326

表4 Power(P_D=0.35(CVD)、α=0.05(両側))

	K (非曝露/曝露)	RR	P_0	P_1	全コホート	m	非曝露群	曝露群	サブコホート	ケース	Power
コホート	0.5	1.5	0.0263	0.0394	3400	-	2267	1133	-	119	0.501
	1	1.5	0.0280	0.0420	3400	-	1700	1700	-	119	0.603
	2	1.5	0.0300	0.0450	3400	-	1133	2267	-	119	0.605
	0.5	1.7	0.0239	0.0406	3400	-	2267	1133	-	119	0.721
	1	1.7	0.0259	0.0441	3400	-	1700	1700	-	119	0.821
	2	1.7	0.0284	0.0482	3400	-	1133	2267	-	119	0.824
	0.5	2	0.0210	0.0420	3400	-	2267	1133	-	119	0.906
	1	2	0.0233	0.0467	3400	-	1700	1700	-	119	0.960
	2	2	0.0263	0.0525	3400	-	1133	2267	-	119	0.962
ケース・コホート	0.5	1.7	0.0239	0.0406	3400	3.025	2267	1133	360	119	0.589
	1	1.7	0.0259	0.0441	3400	3.025	1700	1700	360	119	0.704
	2	1.7	0.0284	0.0482	3400	3.025	1133	2267	360	119	0.715
	0.5	2	0.0210	0.0420	3400	3.025	2267	1133	360	119	0.803
	1	2	0.0233	0.0467	3400	3.025	1700	1700	360	119	0.895
	2	2	0.0263	0.0525	3400	3.025	1133	2267	360	119	0.903
	0.5	2	0.0210	0.0420	3400	1.008	2267	1133	120	119	0.617
	1	2	0.0233	0.0467	3400	1.008	1700	1700	120	119	0.747
	2	2	0.0263	0.0525	3400	1.008	1133	2267	120	119	0.770
	0.5	2	0.0210	0.0420	3400	5.042	2267	1133	600	119	0.845
	1	2	0.0233	0.0467	3400	5.042	1700	1700	600	119	0.923
	2	2	0.0263	0.0525	3400	5.042	1133	2267	600	119	0.928

表5 Power(P_D=0.4(IHD)、α=0.05(両側))

	K (非曝露/曝露)	RR	P_0	P_1	全コホート	m	非曝露群	曝露群	サブコホート	ケース	Power
コホート	0.5	1.5	0.0300	0.0450	3400	-	2267	1133	-	136	0.612
	1	1.5	0.0320	0.0480	3400	-	1700	1700	-	136	0.706
	2	1.5	0.0343	0.0514	3400	-	1133	2267	-	136	0.703
	0.5	1.6	0.0286	0.0457	3400	-	2267	1133	-	136	0.729
	1	1.6	0.0308	0.0492	3400	-	1700	1700	-	136	0.818
	2	1.6	0.0333	0.0533	3400	-	1133	2267	-	136	0.816
	0.5	2	0.0240	0.0480	3400	-	2267	1133	-	136	0.956
	1	2	0.0267	0.0533	3400	-	1700	1700	-	136	0.984
	2	2	0.0300	0.0600	3400	-	1133	2267	-	136	0.984
ケース・コホート	0.5	1.6	0.0286	0.0457	3400	2.647	2267	1133	360	136	0.590
	1	1.6	0.0308	0.0492	3400	2.647	1700	1700	360	136	0.692
	2	1.6	0.0333	0.0533	3400	2.647	1133	2267	360	136	0.696
	0.5	2	0.0240	0.0480	3400	2.647	2267	1133	360	136	0.875
	1	2	0.0267	0.0533	3400	2.647	1700	1700	360	136	0.939
	2	2	0.0300	0.0600	3400	2.647	1133	2267	360	136	0.942
	0.5	2	0.0240	0.0480	3400	0.882	2267	1133	120	136	0.699
	1	2	0.0267	0.0533	3400	0.882	1700	1700	120	136	0.811
	2	2	0.0300	0.0600	3400	0.882	1133	2267	120	136	0.826
	0.5	2	0.0240	0.0480	3400	4.412	2267	1133	600	136	0.910
	1	2	0.0267	0.0533	3400	4.412	1700	1700	600	136	0.960
	2	2	0.03	0.06	3400	4.412	1133	2267	600	136	0.961

厚生労働科学研究費補助金(糖尿病戦略等研究事業)
(分担)研究報告書
糖尿病患者における心血管イベント発症に関する医療経済評価に関する研究
－高脂血症合併症に関する経済評価のためのプロトタイプモデル分析 －

分担 研究者　佐藤貴一郎 国際医療福祉大学・医療経営管理学 客員教授

糖尿病合併症のなかでも重篤な心疾患の発症に関して注目し、わが国で新たに後ろ向きコホート研究を行う臨床研究にもとづき、本分担研究は治療の経済評価によってその有用性を確認すること目的とする。

本年度は現在進行中の臨床評価に先立ち、糖尿病合併高脂血症に関する先行研究 Japan-CDM の成果にもとづき治療効果について、ストロングスタチン投与開始年齢に着目してモデル分析を行い治療の有用性が示唆された。

A. 研究目的

本研究は現在増加傾向にあり国民病となりつつあり、第 5 次医療法改正にて特定された 4 疾患 5 事業の一つである糖尿病の合併症のなかでもリスクの高い心疾患の発症をコントロールする治療の経済評価を行うことを目的としている。本年度は、その中でも糖尿病合併高脂血症患者と虚血性心疾患(IHD)の発症リスクに対する薬物療法に関する疾患の抑制効果を評価するためのコホート分析の基礎となるアセスメントモデルのプロトタイプによるモデル分析を目的とし、治療開始年齢に着目してシミュレーション分析によって発症と患者数推計を試みた。による一次予防効果測定を試みた。

B. 研究方法

1. 研究対象とデータ

全体研究としての糖尿病患者の心疾患発症イベントに関する後ろ向きコホート研究は進行中であり、経済評価のための基礎データは直接利用できる段階ではないため、先行研究としての大規模臨床研究「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」に関する前向きコホート研究の成果をモデル分析の対象とした。

2. 糖尿病高脂血症の IHD 発症と薬物療法に関するモデル分析とシミュレーション

(1)モデル分析の対象患者は先行研究での解析データの平均像である男 67 歳をベースとして、治療開始年齢の差を評価するために、65 歳、70 歳、75 歳で、糖尿病合併高脂血症患者で心血管疾患を罹患していないそれぞれ 10 万人のコホートを想定した。

(2)患者は高脂血症治療薬を服薬中 (脂質管理未達成) 、糖尿症治療経口薬を服薬中であり、LDL-C 値の初期値は先行臨床研究での成績の平均値 158.6mg/dl とした。

(3)抗高脂血症治療薬剤としては先行研究から、最近の傾向を反映して治療ガイドラインでの強化型治療薬であるストロングスタチン(アトルバスチン)を標準とした。

(4)シミュレーション期間は平均余命を考慮して 80 歳までとした。したがって、治療開始年齢にそってそれぞれ 15 年、10 年、5 年間とした。

(5)シミュレーション分析の条件として、

治療薬の効果については、今回 LDL-C のみに注目し、LDL 低下率については JLIT

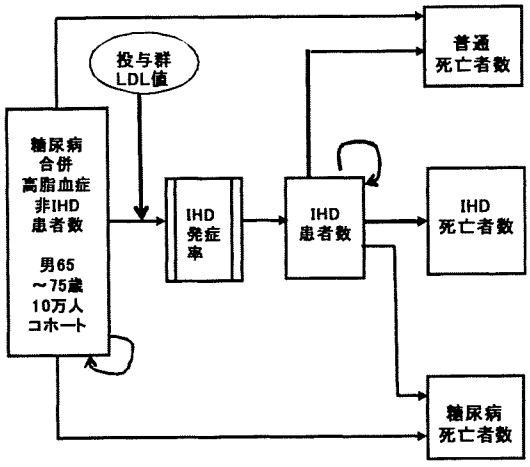
study の成績をモデル化の根拠とし、基本的には投薬後の LDL 低下率は一定で、LDL 値も一定となると仮定した。すなわち、いわゆる従来型のプラバスタチン服用では、 LDL 低下率 1 年目で 20%であるのに対し、「ガイドライン」に沿ったストロングスタチン服用では LDL 低下率 1 年目で30%、以 110mg/dl でフラットとした。

C. 研究結果

1. 虚血性心疾患モデルとシミュレーション

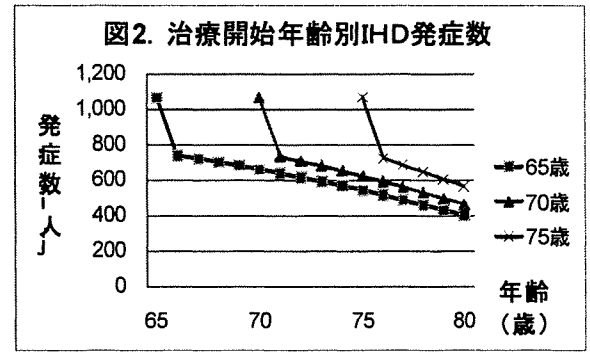
糖尿病患者でイベント発症が多く対応が問題されている虚血性心疾患(IHD)を対象にアセスメントモデルを構築した(図1)。

図1. 糖尿病合併高脂血症薬物療法の IHDアセスメント・プロトタイプモデル概念図



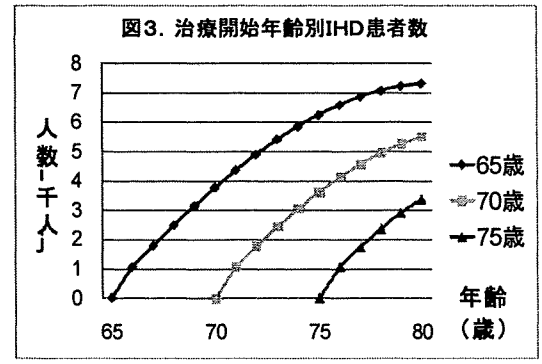
LDL-C 値レベル別 IHD 発症率は Japan-CDM に関する先行研究 1) 登録時のデータを mmol/L 単位から mg/dl 単位に変換したうえ LDL-C 値レベル別発症率をもとに推計した。

治療開始時の各年齢での LDL-C 値と低下傾向が同一条件のもとで IHD の発症数の変化は図2の通りでいずれのケースについても発症数は低下を示している。ただし、初期状態の 1,067 人%から治療薬ストロングスタチンの特性から投与後 1 年後それぞれ 740 人、730 人、720 人へと急激に低下し、その後はいずれの開始年齢別ケースでも発症率が 0.76%に維持されるのに沿った変化を示す。それぞれの発症数の違いは加齢による死亡率の差が反映し、それぞれ 80 歳で、約 405 人、465 人、565 人となる。



＊＊＊

シミュレーション期間の(累積)IHD 患者数は発症数低下を反映して増加率はいずれの治療開始年齢のケースでも逓減している。投与期間が進むほど治療薬の疾患抑制効果があっても LDL-C 値、発症率が同一の条件下では当然ながら投与期間そのもの差が患者数の差に表れ、80 歳時点の累積患者数はそれぞれ 7,300 人、5, 500 人、3, 400 人となる。(図3)。



D. 考察

糖尿病合併高脂血症と糖尿病性心血管症に関する Japan-CDM による臨床研究結果データを適用し、治療ガイドラインにもとづく抗高脂血症治療薬ストロングスタチン投与開始年齢別にモデル分析を行い、いずれの年

齢ケースからもIHDの発症数、累積患者数とも発症リスクの抑制効果により減少が示され高脂血症治療薬の有用性が示された。

但し、今回の分析ではデータの制約から、治療開始年齢にかかわらず初期状態でのLDL-C値が同一としたため、薬剤のLDL-C値抑制効果の特性もあいまって投与期間の進行に対応する発症率も同一となり、低下傾向はほぼ同等となった。患者や治療の実態を考慮すれば、糖尿病合併症のLDL-C値が加齢と無関係とは考えにくく、発症率に影響を与えるはずである。現在進行中の前向きコホート研究結果が待たれるところである。

また、同じくJapan-CDMによる先行研究2)によれば高齢者の糖尿病患者のIHDリスクには低HDL-C値が関係していることが明らかにされている。糖尿病患者に関する高脂血症治療の実態にもとづく経済評価を行いその有用性を確認するためにもやはり現在のコホート研究で標準的治療と臨床効果に関するデータはじめ推計情報が期待される。

E. 結論

糖尿病合併高脂血症患者に関する前向きコホート研究による成果が利用できない状況で、先行したJapan-CDMによる臨床研究結果データを適用し、治療ガイドラインにもとづく抗高脂血症治療薬ストロングスタチン投与開始年齢別にモデル分析を行った。シミュレーション分析によって高脂血症治療薬による糖尿病性の虚血性心疾患は治療開始年齢にかかわらず発症リスクの抑制効果により発症と患者数の減少があきらかになり医療経済的な効果が示唆された。

ただし、データの制約上必ずしも実態を反映した条件下で分析が行えなかった。今後、前向きコホート研究の進捗に応じて医療経済評価の制度が向上すると期待される。

<参照文献>

1) Toshio Hayashi 他、Importance of Lipid Levels in Elderly Diabetic Individuals、Circ J 2008;72:218-225

2) Toshio Hayashi 他、Low HDL Cholesterol Is Associated With the Risk of Stroke in Elderly Diabetic Individuals、Diabetes Care, 2009;32(7):1221-1223

厚生労働科学研究費補助金
分担研究報告書

研究成果での国立国際医療センターでのデータ登録

分担研究者　能登 洋　（国立国際医療センター戸山病院・糖尿病・代謝症候群診療部
医療連携統括室医長）

研究要旨
林班の研究における患者登録データを、当センター糖尿病情報センターのデータベースへの登録を可能にすべく両者のマッチングを考察した。

A.　研究目的

平成 19 年の「糖尿病等の生活習慣病対策の推進に関する検討会」において、拠点機関が臨床データを収集・分析することの重要性が指摘され、これに基づいて、平成 20 年度より開始された厚生労働科学研究「糖尿病診療均てん化のための標準的診療マニュアル作成とその有効性の検証」（研究代表者 笹月健彦 国立国際医療センター前 総長）では、「標準化された診療データの収集・蓄積システムの提起、それによる臨床研究遂行体制の構築」という目標が盛り込まれている。当センターではこの目標を具現化し、その活用の一環として糖尿病患者における心血管疾患のリスク評価のために林班研究のデータを有効に登録することを目的とする。

B.　研究方法

国立国際医療センター戸山病院において、糖尿病情報センター事業として進行中である糖尿病患者データベースに患者情報を EXCEL のマクロプログラムを用いて入力できるツール・インターフェイスを構築する。

（倫理面への配慮）登録する患者情報はあくまで既存の診療情報であり、計画的に特定の診療情報を得ようとするものではない。本年度得られた情報について、各施設においてカルテ ID を匿名化し、カルテ ID と匿名化 ID は各施設で保存し外部には持ち出さない。氏名は情報に含まれず、最終的に糖尿病情報データベースに登録されるのは連結可能匿名化された情報である。

C.　研究結果

糖尿病情報センターでは以下に示す患者情報を登録する入力ツールを開発し、登録を開始した。さらに林班の研究における患者登録データを、そのデータベースへ登録可能となるよう両者のマッチングを考察した。現在各専門分野の分担研究者によりイベントの設定および判定基準作成を行っている。

登録項目：基本情報
指導情報
治療履歴（治療内容・合併症・検査所見を含む）

D.　考察

イベントの判定について、現在各原案を検討中であるが、きちんとした判定基準を満たすか

どうかについては、糖尿病情報データベースにおいて要求されている項目のみでは不十分な分野もあり、両者のマッチングについて検討を継続し、効率的なデータ入力体制を構築する必要があると思われる。

E. 結論

イベント発生登録およびリスク因子の解析を行うために、登録患者において林班研究の後ろ向きデータ登録を推進し、整合性を極力増やす努力が必要と考えられる。

F. 研究発表

能登 洋・野田 光彦。糖尿病診療ガイドライン・レビュー。MindsPLUS／医療提供者向け／CPG レビュー。
http://minds.jcqhc.or.jp/stc/0004/4/0004_G0000077_T0003027.html 2009 年。

G. 知的所有権の取得状況

なし

厚生労働科学研究費補助金
分担研究報告書

高齢糖尿病患者の認知機能低下に関連する因子

研究分担者　梅垣宏行　（名古屋大学医学部附属病院老年内科　助教）

研究要旨
高齢糖尿病患者の認知機能低下に関連する因子を明らかにするために、非認知症の高齢糖尿病患者を３年間観察し認知機能の低下に関連する因子を検討した。非認知症の高齢２型糖尿病患者の血糖と血中インスリンの高値は、３年後の認知機能の低下と関連することが明らかになった。

A. 研究目的

高齢者における２型糖尿病は認知機能低下や認知症発症の危険因子であることが明らかになってきた。しかしながら、高齢２型糖尿病患者の認知機能について縦断的に検討した報告はほとんどない。今回我々は、非認知症の高齢糖尿病患者を３年間観察し認知機能の低下に関連する因子を明らかにすることを目的とした。

B. 研究方法

６５歳以上の２型糖尿病患者でMMSEが２４点以上のもの、５５名（男性２３名、女性３２名）を３年間フォローした。ベースラインでの平均年齢は74.4±5.7歳、平均HbA1cは6.7±0.8%であった。ベースラインと観察終了時に認知機能を評価した。認知機能評価のための神経心理検査としては、MMSE、ADASの単語再生課題（即時および遅延）、Digit Symbol Substitution Test (DSST)、Stroop testである。抑うつ度の評価としてはGeriatric Depression Scale （GDS）の短縮版であるGDS-15を用いた。
神経心理検査の成績の変化とベースラインの各種因子との関係を multiple regression analysisにて解析した。
（倫理面への配慮）
参加者は十分な説明をうけ、書面による同意を得た。データは匿名化された状態で解析され、個人情報の保護には充分配慮をした。

C.研究結果

ベースラインの MMSE の平均は 26.7±2.2 点で、３年後には平均2.6±3.5 点低下した。年齢、教育歴、BMI、GDS-15、ベースラインの各神経心理検査の成績で調整した multiple regression analysis では、血中インスリン値とMMSEの変化と負の関連を認めた。同様に DSST と Stroop の成績の変化はHbA1cと負の関連を認めた。

D.考察

高齢糖尿病患者の認知機能低下については、近年注目が集まっており、多くのデータが集積されつつあるが、そのほとんどが横断的な解析であり、縦断的な解析のデータはあまりない。本研究では、登録時のHbA1cによって評価された血糖コントロールの不良や、高インスリン血症が３年後の認知機能低下と有意に関連していたことは重要と考えられ、今後その機序の解明が必要である。

E.結論

非認知症の高齢 2 型糖尿病患者の血糖と血中インスリンの高値は、３年後の認知機能の低下と関連した。

F.研究発表

１．論文発表

Umegaki H, Iimuro S, Araki A, Sakurai T, Iguchi A, Ohashi Y, Ito H.
Association of higher carbohydrate intake with depressive mood in elderly diabetic women.
Nurtritional Neuroscience, 2009 in press

Umegaki H
Pathophysiology of cognitive dysfunction in older people with type 2 diabetes: vascular changes or neurodegeneration?
Age and Ageing, 2010 in press

２．学会発表

平成 22 年日本老年医学会学術集会にて発表予定

G. 知的所有権の取得状況

なし

Ⅲ．研究成果の刊行に関する一覧表

別紙４

研究成果の刊行に関する一覧表

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Hayashi T, Kawashima S, Itoh H, Yamada N, Sone H, Watanabe H, Hattori Y, Ohrui T, Yokote K, Nomura H, Umegaki H, Iguchi A .	Low HDL-cholesterol is associated with the risk of stroke in elderly diabetic individuals: Changes in the risk for atherosclerotic diseases at various ages.	*Diabetes Care*	32:	1221-1223,	2009.
Ito H, Araki A,	Diabetes mellitus and Geriatric syndromes	*Geriatrics Gerontology*	9:	105-114	2009
Hattori Y,et al	Cilostazol inhibits cytokine-induced nuclear factor-(kappa)B activationvia AMP-activated protein Kinase activation in vascular endothelial cells	*Cardiovasc Res*	81:	133-138	2009
Asamura T, Ohrui T,et al.	Centrally active ACELs and cognitive decline.	*Archives of Internal Medicine*	170:	107-108,	2010.
Yokote K, Saito Y,	Influence of statins on Glucose tolerance in Patients with type 2 Diabetes mellitus: subanalysis of the collaborative study on hypercholesterolemia drug intervention and their benefits For atherosclerosis prevention(CHIBA study).	*J Attheroscler Thromb*	16:	297-298,	2009.
Kutluk A, Tsuji T, Ukawa T, Nakamura R, Saeki N, Yoshizumi M, Kawamoto M	A novel online method to monitor autonomic nervous activity based on arterial wall impedance and heart rate variability.	Med Biol Eng Comput.		[Epub ahead of print]	2010
Kodama S, Saito K, Tanaka S, Maki M, Yachi Y, Asumi M, Sugawara A, Totsuka K, Shimano H, Ohashi Y, Yamada N, Sone H.	Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women.	*JAMA*	301:	2024-2035,	2009.

Kawai K, Kawashima S, Miyazaki T et al.	Serum beta2-microglobulin concentration as a novel marker to distinguish Levels of risk in acute Heart failure patients	*J Cardiol*	55:	99-107,	2010.
Umegaki H,	Pathophysiology of cognitive dysfunction in older People with type 2 diabetes:vascular changes or neurodegeneration?	*Age and Ageing*	39:	8-10,	2010.

Ⅳ.研究成果の刊行物・別冊

Low HDL Cholesterol Is Associated With the Risk of Stroke in Elderly Diabetic Individuals

Changes in the risk for atherosclerotic diseases at various ages

TOSHIO HAYASHI, MD, PHD[1]
SEINOSUKE KAWASHIMA, MD, PHD[2]
HIDEKI ITOH, MD, PHD[3]
NOBUHIRO YAMADA, MD, PHD[4]
HIROHITO SONE, MD, PHD[5]
HIROSHI WATANABE, MD, PHD[6]
YOSHIYUKI HATTORI, MD, PHD[7]
TAKASHI OHRUI, MD, PHD[8]
KOUTARO YOKOTE, MD, PHD[9]
HIDEKI NOMURA, MD, PHD[10]
HIROYUKI UMEGAKI, MD, PHD[1]
AKIHISA IGUCHI, MD, PHD[1]
ON BEHALF OF THE JAPAN CDM GROUP

OBJECTIVE — To clarify the relationship between lipid levels and ischemic heart disease (IHD) and cerebrovascular disease (CVD) in diabetic individuals.

RESEARCH DESIGN AND METHODS — The Japan Cholesterol and Diabetes Mellitus Study is a prospective cohort study of 4,014 type 2 diabetic patients (1,936 women; mean ± SD age 67.4 ± 9.5 years). Lipid and glucose levels and other factors were investigated in relation to occurrence of IHD or CVD.

RESULTS — IHD and CVD occurred in 1.59 and 1.43% of participants, respectively, over a 2-year period. The relation of lower HDL or higher LDL cholesterol to occurrence of IHD in subjects <65 years old was significant. Lower HDL cholesterol was also significantly related to CVD in subjects ≥65 years old and especially in those >75 years old (n = 1,016; odds ratio 0.511 [95% CI 0.239–0.918]; $P < 0.05$). Stepwise multiple regression analysis with onset of CVD as a dependent variable showed the same result.

CONCLUSIONS — Lower HDL cholesterol is an important risk factor for not only IHD but also CVD, especially in diabetic elderly individuals.

Diabetes Care 32:1221–1223, 2009

Type 2 diabetes, dyslipidemia, and aging are independent risk factors for cardiovascular diseases. Japanese individuals have lower rates of ischemic heart disease (IHD) and higher rates of cerebrovascular disease (CVD); however, diabetic individuals have an increased risk of IHD (1,2). Risk factors for IHD or CVD in elderly diabetic individuals are not fully known (3), and the Japan Cholesterol and Diabetes Mellitus Study was formulated to evaluate them (Umin Clinical Trials Registry, clinical trial reg. no. UMIN00000516; http://www.umin.ac.jp/ctr/index.htm).

RESEARCH DESIGN AND METHODS

— The Japan Cholesterol and Diabetes Mellitus Study is a single-center prospective cohort study comprised of 4,014 Japanese diabetic individuals on a consecutive outpatient basis recruited between September 2004 and March 2005 (1,936 women; mean ± SD age 67.4 ± 9.5 years [range 35–83 years]). Patients with previous IHD (myocardial infarction, unstable angina pectoris, angioplasty, or bypass grafting) or CVD (stroke) were excluded. Follow-up information was available for 98.2 and 92.3% of patients enrolled in the first and second years, respectively. Patients were divided into those aged <65 years, 65–74 years, and >75 years (n = 1,267, 1,731, and 1,016, respectively). The primary end points were onset of IHD or CVD. Plasma lipid, glucose, A1C, and other relevant levels were measured annually.

The study was approved by institutional review boards and by the safety-monitoring board. All events were confirmed by the organizing committee annually. The guidelines of the Japan Atherosclerosis Society (2002), stating that LDL cholesterol should be <120 mg/dl and HDL cholesterol >40 mg/dl in diabetic individuals, and the American Diabetes Association criteria for diagnosis of type 2 diabetes were used (4,5).

Results are presented as means ± SD. All statistical analyses were performed using JMP software (SAS Institute, Cary, NC). Incidences were analyzed in relation to risk factors. Univariate and multiple logistic regression analysis and stepwise analysis were used. Values of $P < 0.05$ were considered significant.

RESULTS

— Mean A1C, fasting plasma glucose, LDL cholesterol, triglyceride, HDL cholesterol, and systolic and diastolic blood pressure levels on registration were 7.53 ± 1.12%, 159.4 ± 52.7

From the [1]Department of Geriatrics, Nagoya University Graduate School of Medicine, Nagoya, Japan; the [2]Division of Cardiovascular and Respiratory Medicine, Department of Internal Medicine, Kobe University Graduate School of Medicine, Kobe, Japan; the [3]Tokyo Metropolitan Geriatric Hospital, Tokyo, Japan; the [4]Department of Internal Medicine, Endocrinology and Metabolism, Graduate School of Comprehensive Human Sciences, University of Tsukuba, Tsukuba, Japan; the [5]Department of Nutrition, Ochanomizu University, Tokyo, Japan; the [6]Department of Clinical Pharmacology and Therapeutics, Hamamatsu University School of Medicine, Hamamatsu, Japan; the [7]Department of Endocrinology and Metabolism, Dokkyo University School of Medicine, Mibu, Japan; the [8]Department of Geriatric Medicine, Tohoku University School of Medicine, Sendai, Japan; the [9]Division of Diabetes, Metabolism and Endocrinology, Department of Internal Medicine, Chiba University Hospital, Chiba, Japan; and the [10]Department of Geriatrics, Nagoya Kita Hospital, Nagoya, Japan.
Corresponding author: Toshio Hayashi, hayashi@med.nagoya-u.ac.jp.
Received 18 September 2008 and accepted 7 January 2009.
Published ahead of print at http://care.diabetesjournals.org on 8 June 2009. DOI: 10.2337/dc08-1677.

Table 1—*Adjusted multiple regression analyses of factors found to be significant by univariate regression analysis for IHD or CVD, as well as major atherogenic risk factors; total* n = *4,014*

	<65 years old (*n* = 1,276)		65–74 years old (*n* = 1,731)		≤75 years old (*n* = 1,016)	
	Adjusted OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*
IHD						
Sex	1.469 (1.02–1.94)	0.02*	1.109 (1.02–1.74)	0.04*	0.829 (0.23–3.06)	0.78
Age	1.063 (0.96–1.20)	0.28	0.991 (0.86–1.15)	0.99	0.996 (0.83–1.17)	0.87
LDL cholesterol	1.225 (1.02–2.04)	0.04*	1.001 (0.72–1.25)	0.89	0.776 (0.43–1.40)	0.40
HDL cholesterol	0.659 (0.39–0.98)	0.04*	0.939 (0.68–1.25)	0.38	0.946 (0.58–1.29)	0.23
Triglycerides	1.356 (1.00–2.02)	0.05	0.731 (0.52–1.94)	0.18	0.881 (0.46–1.70)	0.71
A1C	1.179 (0.75–1.88)	0.27	1.082 (0.76–1.55)	0.67	1.274 (0.57–2.35)	0.44
SBP	0.702 (0.49–1.09)	0.15	1.082 (0.79–1.69)	0.15	1.051 (0.58–1.89)	0.87
DBP	1.020 (0.97–1.05)	0.28	1.088 (0.73–1.27)	0.24	1.998 (0.99–4.35)	0.08
CVD						
Sex	1.158 (0.68–2.17)	0.47	1.004 (0.79–1.69)	0.82	0.847 (0.45–1.52)	0.58
Age	1.006 (0.94–1.10)	0.88	0.982 (0.82–1.14)	0.39	1.139 (0.99–1.30)	0.06
LDL cholesterol	1.099 (0.98–1.23)	0.06	1.067 (0.76–1.44)	0.51	1.128 (0.64–1.59)	0.71
HDL cholesterol	0.888 (0.64–1.48)	0.09	0.758 (0.53–0.98)	0.04*	0.511 (0.24–0.92)	0.04*
Triglycerides	1.147 (0.68–2.04)	0.62	1.070 (0.69–1.67)	0.75	1.355 (0.75–2.56)	0.32
A1C	0.996 (0.64–1.28)	0.52	1.019 (0.75–1.74)	0.54	1.015 (0.60–1.72)	0.95
SBP	1.005 (0.67–1.33)	0.86	0.991 (0.94–1.13)	0.35	1.063 (0.62–1.57)	0.75
DBP	1.109 (0.61–2.13)	0.74	1.303 (0.81–2.09)	0.27	1.045 (0.68–1.5)	0.59

	IHD				CVD			
	<65 years old	65–74 years old	≤75 years old	Total	<65 years old	65–74 years old	≤75 years old	Total
HDL cholesterol (mg/dl)								
<44	2.31	2.49	1.68	2.14	1.13	1.99	2.62*	2.01
44–53	1.45	1.45	1.64	1.50	1.05	1.84	2.15*	1.64
54–63	1.25	1.41	0.98	1.23	1.44	0.80	0.88*	1.04
≥64	0.42	1.69	0.99	1.19	1.0	0.80	0.45*	0.72

Data were adjusted for sex. The ratio of male to female subjects is 1:1. *Statistically significant ($P < 0.05$). DBP, diastolic blood pressure; SBP, systolic blood pressure.

mg/dl, 120.3 ± 32 mg/dl, 140.6 ± 108.3 mg/dl, 55.8 ± 18.0 mg/dl, 136.5 ± 17.1 mmHg, and 75.1 ± 11.1 mmHg, respectively. Insulin and oral agents for diabetes were prescribed for 19.9 and 70.5% of individuals, respectively. Dyslipidemia was seen in 79.1%, and antihyperlipidemic drugs were prescribed in 59.0%. Mean lipid and glucose metabolism levels did not change significantly over the 2-year study period.

In the first and second years, 83 and 69 vascular events occurred, respectively. IHD and CVD occurred in 0.80 and 0.71% of total patients per year. The relationship between IHD or CVD and background factors such as LDL cholesterol levels in each age-group was analyzed by univariate logistic regression.

Sex, age, LDL cholesterol, HDL cholesterol, and triglyceride were significantly related to IDH in patients aged <65 years. Age, sex, history of hypertension, and antihypertensive drugs were related in patients aged between 65 and 74 years, and sex and systolic and diastolic blood pressure were related in patients aged > 75 years. CVD and LDL cholesterol were related in patients aged <65 years, and HDL cholesterol and systolic blood pressure were related in patients aged >75 years.

We performed multiple regression analysis with factors found to be significant by univariate regression analysis for IHD or CVD and other atherogenic risk–related factors (A1C, etc.) in three age-groups (Table 1). LDL and HDL cholesterol were associated with IHD in patients aged < 65 years but not in other age-groups. Sex was associated with IHD in individuals aged <74 years. HDL cholesterol was also associated with CVD in individuals between aged between 65 and 74 years and >75 years.

Stepwise multiple regression analysis was performed using factors that were found to be significant by univariate regression analysis for IHD or CVD and other atherogenic risk–related factors. HDL and LDL cholesterol were associated with IHD in individuals aged <65 years (HDL cholesterol odds ratio 0.79 [95% CI 0.58–0.96; $P = 0.04$] and LDL cholesterol 0.60 [0.33–0.99; $P = 0.04$]). HDL cholesterol was associated with CVD in individuals aged between 65 and 74 years and ≥75 years (65–74 years 0.73 [0.56–0.94; $P = 0.04$] and ≥75 years 0.60 [0.35–0.91; $P = 0.01$]).

The relation of age or HDL cholesterol to IHD and CVD was evaluated in quartile categories. HDL cholesterol levels were inversely correlated with IHD in individuals aged <65 years (hazards ratio 0.633 [95% CI 0.428–0.975]) but not in other groups. The relationship between CVD and HDL cholesterol was prominent in those aged >75years but not in other age-groups (Table 1). There were no sex-related differences in the relationship of HDL cholesterol with CVD. There was no relationship between LDL, triglyceride, fasting blood glucose, or A1C and the frequency of CVD.

CONCLUSIONS — This study represents one of the largest-scale attempts to examine IHD and CVD in middle-aged and elderly diabetic individuals. In the U.S., evidence suggests that middle-aged diabetic individuals have an IHD risk similar to that for individuals with myocardial infarction (6). However, this risk may not exist in elderly diabetic individuals. Many guidelines to prevent atherothrombotic diseases recommend strict control of LDL cholesterol in diabetic patients but the same guideline for HDL cholesterol control (40 mg/dl) as that used for nondiabetic subjects (4–7).

A novel finding was that type 2 diabetic elderly individuals had frequent CVD, and incidence rates were associated with HDL cholesterol. Few data were available for the relationship among elderly, type 2 diabetes, and CVD (8,9).

There have been three large-scale clinical studies of statins that included participants aged up to 75 years (10–12). Although they reported that statins exerted effects on IHD (including in diabetic individuals), effects were not pronounced. (Prosper reported that statins induced a 16% decrease in IHD without any effects on CVD.) The data suggest that because LDL cholesterol decreased, simple LDL cholesterol control may not prevent IHD or CVD in elderly individuals. Our study shows the importance of HDL cholesterol in CVD in elderly diabetic individuals and in IHD in middle-aged diabetic individuals. If HDL cholesterol is well controlled in elderly diabetic patients, then CVD and IHD might be decreased to the levels found in middle-aged cohorts. Patients prescribed statins whose HDL cholesterol was <40 mg/dl showed the same risk (data not shown). Although medicated patients may be more conscious of diseases, HDL cholesterol is a strong risk factor and masks the effects of statins.

In conclusion, HDL and LDL cholesterol were risk factors for IHD in diabetic patients aged <65 years. In addition, HDL cholesterol was a risk factor for CVD in elderly diabetic subjects, especially those aged >75 years. HDL cholesterol may help prevent CVD in elderly diabetic subjects. Risk factors for IHD and CVD appear to change with advancing age.

Acknowledgments— This study was supported by the Japanese Ministry of Health, Welfare and Labor.

No potential conflicts of interest relevant to this article were reported.

References

1. Kubo M, Kiyohara Y, Kato I, Tanizaki Y, Arima H, Tanaka K, Nakamura H, Okubo K, Iida M. Trends in the incidence, mortality, and survival rate of cardiovascular disease in a Japanese community: the Hisayama study. Stroke 2003;34:2349–2354
2. Sone H, Mizuno S, Ohashi Y, Yamada N. Type 2 diabetes prevalence in Asian subjects. Diabetes Care 2004;27:1251–1252
3. Valensi P, Pariès J, Brulport-Cerisier V, Torremocha F, Sachs RN, Vanzetto G, Cosson E, Lormeau B, Attali JR, Maréchaud R, Estour B, Halimi S. Predictive value of silent myocardial ischemia for cardiac events in diabetic patients: influence of age in a French multicenter study. Diabetes Care 2005;28:2722–2727
4. Hata Y, Mabuchi H, Saito Y, Itakura H, Egusa G, Ito H, Teramoto T, Tsushima M, Tada N, Oikawa S, Yamada N, Yamashita S, Sakuma N, Sasaki J, the Working Committee on JAS Guideline for Diagnosis and Treatment of Hyperlipidemias. Report of the Japan Atherosclerosis Society (JAS) Guideline for Diagnosis and Treatment of Hyperlipidemia in Japanese adults. J Atheroscler Thromb 2002;9:1–27
5. American Diabetes Association Consensus Panel. Guidelines for computer modeling of diabetes and its complications. Diabetes Care 2004;27:2262–2265
6. IDF Clinical Guidelines Task Force. Global guideline for type 2 diabetes: recommendations for standard, comprehensive, and minimal care. Diabet Med 2006; 23:579–593
7. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 2001;285: 2486–2497
8. Marshall SM, Flyvbjerg A. Prevention and early detection of vascular complications of diabetes. BMJ 2006;333:475–480
9. Ratner R, Goldberg R, Haffner S, Marcovina S, Orchard T, Fowler S, Temprosa M, the Diabetes Prevention Program Research Group. Impact of intensive lifestyle and metformin therapy on cardiovascular disease risk factors in the diabetes prevention program. Diabetes Care 2005;28: 888–94
10. Shepherd J, Blauw GJ, Murphy MB, Bollen EL, Buckley BM, Cobbe SM, Ford I, Gaw A, Hyland M, Jukema JW, Kamper AM, Macfarlane PW, Meinders AE, Norrie J, Packard CJ, Perry IJ, Stott DJ, Sweeney BJ, Twomey C, Westendorp RG, the PROSPER Study Group. PROspective Study of Pravastatin in the Elderly at Risk (PROSPER): a randomized controlled trial. Lancet 2002;360:1623–1630
11. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomized placebo-controlled trial. Lancet 2002;360:7–22
12. Sever PS, Poulter NR, Dahlöf B, Wedel H, Collins R, Beevers G, Caulfield M, Kjeldsen SE, Kristinsson A, McInnes GT, Mehlsen J, Nieminen M, O'Brien E, Ostergren J. Reduction in cardiovascular events with atorvastatin in 2,532 patients with type 2 diabetes: Anglo-Scandinavian Cardiac Outcomes Trial–lipid-lowering arm (ASCOT-LLA). Diabetes Care 2005;28: 1151–1157

COMMENTS AND OPINIONS

Designing Appropriate Clinical Trials to Assess ACEI Use and Cognitive Decline in Older Adults With Hypertension

Sink et al[1] report that exposure to angiotensin-converting enzyme inhibitors (ACEIs) is not associated with dementia risk or cognitive decline in older hypertensive adults compared with other antihypertensive drugs. Centrally active ACEIs, ie, those that cross the blood-brain barrier (BBB) (animal data), reduced cognitive decline, whereas noncentrally acting ACEIs (BBB impermeable) were associated with greater risk of incident dementia and disability in instrumental activities of daily living.[1] These effects were independent of blood pressure regulation and prompted a call for a randomized clinical trial of centrally active ACEIs in the prevention of cognitive decline and dementia.[1]

Controversies remain. Angiotensin-converting enzyme inhibitors modulate progression of amnestic mild cognitive impairment.[2] With the analysis limited to dihydropyridines or diuretics, significant benefits on dementia are suggested.[3] The only study in older hypertensive patients to show a significant effect was nitrendipine based.[3] A recent study found that any antihypertensive medication, but particularly potassium-sparing diuretics, was associated with lower risks for Alzheimer disease (AD).[3] The most recent study findings in very elderly people, involving perindopril and indapamide, were negative.[4]

In their discussion, Sink et al[1] fail to make the point that the intervention in the Perindopril Protection Against Recurrent Stroke Study (PROGRESS) was perindopril based, ie, treatment was perindopril plus indapamide (received by 58% of subjects). Therefore, an effect could not be concluded to be on the basis of perindopril use alone.[3] The design of hypertension studies was not powered primarily on the outcome of cognition or dementia. The following unresolved issues remain: Does treatment of hypertension in middle age reduce cognitive decline and/or dementia in late-life? Does treatment of hypertension in older adults reduce cognitive decline and the risk of dementia? Are any benefits associated with a specific regimen? Future studies must have cognition and dementia as a primary outcome. Given that the study population is relatively cognitively normal, the optimal study design should include specific tests of attention, episodic memory, and other measures of executive function.[5] It may be possible to examine the effects of individual agents within those designs but the numbers required are likely to be very large. The important issue of equivalent blood pressure control in comparative groups compared with the treatment regimen is problematic but achievable. With the current focus on management of overall cardiovascular risk, studies must factor in the use of antiplatelet, lipid-lowering, and other interventions. Perhaps the priority area for study, given the increasing awareness of the interface between AD and cardiovascular risk factors, is the role of modulation of cardiovascular risk on disease progress in patients with established AD.

Stephen Todd, MD, MRCP
Bernadette McGuinness, MD, MRCP
A. Peter Passmore, MD, FRCP, FRCPI

Correspondence: Dr Todd, Ageing Group, Centre for Public Health, School of Medicine, Dentistry and Biomedical Sciences, The Queen's University of Belfast, Whitla Medical Building, 97 Lisburn Rd, Belfast BT9 7BL, Ireland (s.todd@qub.ac.uk).

Funding/Support: Drs Todd and McGuinness have each received an award from the Paul B. Beeson Career Development Awards in Aging Research Program for the Island of Ireland.

1. Sink KM, Leng X, Williamson J, et al. Angiotensin-converting enzyme inhibitors and cognitive decline in older adults with hypertension: results from the cardiovascular health study. *Arch Intern Med*. 2009;169(13):1195-1202.
2. Rozzini L, Chilovi BV, Bertoletti E, et al. Angiotensin converting enzyme (ACE) inhibitors modulate the rate of progression of amnestic mild cognitive impairment. *Int J Geriatr Psychiatry*. 2006;21(6):550-555.
3. McGuinness B, Todd S, Passmore P, Bullock R. The effects of blood pressure lowering on development of cognitive impairment and dementia in patients without apparent prior cerebrovascular disease. *Cochrane Database Syst Rev*. 2006;(2):CD004034.
4. Peters R, Beckett N, Forette F, et al; HYVET investigators. Incident dementia and blood pressure lowering in the hypertension in the very elderly trial cognitive function assessment (HYVET-COG): a double-blind, placebo controlled trial. *Lancet Neurol*. 2008;7(8):683-689.
5. Saxby BK, Harrington F, McKeith IG, Wesnes K, Ford GA. Effects of hypertension on attention, memory, and executive function in older adults. *Health Psychol*. 2003;22(6):587-591.

Centrally Active ACEIs and Cognitive Decline

We read with interest the article by Sink and colleagues[1] describing an association between the use of centrally active ACEIs that can cross the BBB and a reduction in cognitive decline in a large, well-characterized cohort of treated older adults with hypertension. Using computerized information on patients in our university hospital, we also found that the long-term use of centrally active ACEIs (captopril or perindopril) is associated with a lower risk of incident dementia compared with other antihypertension drugs in elderly hypertensive patients.[2] Furthermore, we found that the centrally active ACEIs significantly reduce the

rate of cognitive decline in hypertensive patients with mild to moderate AD compared with other antihypertensive drugs, although all participants had a stable and comparable blood pressure.[3]

Of greatest concern is whether the centrally active ACEIs can actually cross the BBB in humans. In this article, ACEIs were classified into 2 groups according to their ability to cross the BBB based primarily on experiments in rats.[1] We examined whether administration of perindopril, a centrally active ACEI, can alter cerebrospinal fluid (CSF) angiotensin-converting enzyme activity in hypertensive patients with AD. We measured CSF angiotensin-converting enzyme activity before and 1 month after oral administration of perindopril (2 mg/d) and found that perindopril significantly inhibited CSF angiotensin-converting enzyme activity in hypertensive patients with AD (mean [SE] CSF angiotensin-converting enzyme level in 7 patients, 0.24 [0.02] [before] vs 0.13 [0.03] IU/L [after]; $P=.04$).[4] These results suggest that perindopril might actually cross the BBB and directly modify the renin-angiotensin system in the human brain.

The results of our study provide additional support for the conclusion by Sink et al[1] that the centrally active ACEIs are associated with a lower risk of cognitive decline via mechanisms other than blood pressure control. Physicians should consider specific tissue distribution of ACEIs with the hope of correlating these with actions in vivo that might be of clinical significance.

Takaaki Asamura, MD
Takashi Ohrui, MD
Kaori Une, MD
Katsutoshi Furukawa, MD
Hiroyuki Arai, MD

Correspondence: Dr Ohrui, Department of Geriatrics and Gerontology, Institute of Development, Aging and Cancer, Tohoku University, 4-1 Seiryo-machi, Aoba-ku, Sendai 980-8575, Japan (ohruit@idac.tohoku.ac.jp).

1. Sink KM, Leng X, Williamson J, et al. Angiotensin-converting enzyme inhibitors and cognitive decline in older adults with hypertension: results from the Cardiovascular Health Study. *Arch Intern Med*. 2009;169(13):1195-1202.
2. Ohrui T, Matsui T, Yamaya M, et al. ACE inhibitors and incidence of Alzheimer's disease in Japan. *J Am Geriatr Soc*. 2004;52(4):649-650.
3. Ohrui T, Tomita N, Sato-Nakagawa T, et al. Effects of brain-penetrating ACE inhibitors on Alzheimer disease progression. *Neurology*. 2004;63(7):1324-1325.
4. He M, Ohrui T, Maruyama M, et al. ACE activity in CSF of patients with mild cognitive impairment and Alzheimer disease. *Neurology*. 2006;67(7):1309-1310.

In reply

We thank Asamura and colleagues for their letter and agree that physicians should consider tissue distribution when selecting an ACEI. Todd and colleagues point out that the intervention in the PROGRESS trial was perindopril based and for some participants also included indapamide. However, this was a placebo-controlled trial and 2561 participants were randomized to single therapy with perindopril or placebo, thus allowing a direct comparison to be made. In that subgroup analysis, there was a 15% risk reduction for cognitive decline in the perindopril group, though it did not reach statistical significance.[1] We agree with Todd and colleagues that there are still many questions to be answered in the connection between hypertension and cognitive impairment or dementia and specific antihypertensive regimens and agree that designing studies of hypertension treatment powered on the primary outcome of cognition is an important next step, as we highlighted in our discussion.[2] In the meantime, when starting an ACEI therapy for hypertension, clinicians might consider preferentially using one that crosses the BBB.

Kaycee M. Sink, MD, MAS
David C. Goff Jr, MD, PhD

Correspondence: Dr Sink, Internal Medicine, Wake Forest University School of Medicine, Sticht Center on Aging, Medical Center Boulevard, Winston-Salem, NC 27157 (kmsink@wfubmc.edu).

1. Tzourio C, Anderson C, Chapman N, et al; PROGRESS Collaborative Group. Effects of blood pressure lowering with perindopril and indapamide therapy on dementia and cognitive decline in patients with cerebrovascular disease. *Arch Intern Med*. 2003;163(9):1069-1075.
2. Sink KM, Leng X, Williamson J, et al. Angiotensin-converting enzyme inhibitors and cognitive decline in older adults with hypertension: results from the Cardiovascular Health Study. *Arch Intern Med*. 2009;169(13):1195-1202.

Concerns About Heparin Therapy for Hypertriglyceridemia

Chylomicronemia is a major component of the most severe hypertriglyceridemia (HTG) and is commonly associated with diabetes mellitus (DM). In the August 10/24 issue of the *Archives*, Cole[1] described the management approach for one such patient treated with low-level intravenous unfractionated heparin (UFH). This patient had a timely decrease in plasma triglyceride (TG) level, and UFH therapy was credited with the successful outcome. However, the patient received insulin initially. In his brief review of previous reports of heparin treatment for severe HTG, Cole[1] cites 9 references, but only 2 (Loo and Tan[2]; Sleth et al[3]) did not also administer insulin. Insulin is well established as a cofactor of lipoprotein lipase (LPL) and may contribute markedly to lipolysis of chylomicrons and very low-density lipoproteins.[4] Lipoprotein lipase is bound to heparan sulfate proteoglycans (very similar to heparin) on capillary walls, which is where the LPL hydrolyzes TGs in chylomicrons and very low-density lipoproteins.[5] The intravenous injection of UFH produces a rapid increase in circulating LPL, then the lipolysis system appears to circulate as a heparin-apoenzyme complex followed by an exponential disappearance of LPL activity.[6] The inactivation system involves the destruction of heparin by a liver heparinase and subsequent dissociation of the active complex followed by removal of the apoenzyme.[6] Concerns must be raised regarding any protocol using UFH to treat severe HTG because when additional UFH is added to the assay system, human LPL released by UFH develops a marked *decrease* in activity.[7] In his observation, Cole[1] notes that longer-term heparin can decrease LPL concentration if hepatic metabolism and degradation are greater than production and release of LPL.

Geriatr Gerontol Int 2009; 9: 105–114

REVIEW ARTICLE

Diabetes mellitus and geriatric syndromes

Atsushi Araki and Hideki Ito

Department of Endocrinology, Tokyo Metropolitan Geriatric Hospital, Tokyo, Japan

Diabetes mellitus is associated with an increased prevalence and incidence of geriatric syndrome: functional disabilities, depression, fall, urinary incontinence, malnutrition and cognitive impairment. Geriatric syndrome not only leads to frailty, loss of independence and low quality of life, but also becomes a major obstacle in the treatment and care of diabetic people. The risk factors or contributing factors of geriatric symptoms are micro- and macrovascular complications, age-rated comorbid disease and aging per se. Comprehensive geriatric assessment of geriatric syndrome, including basic activities of daily living, instrumental activities of daily living, gait and balance, visual acuity, the Mini-Mental State Examination, depression scores, history and risk of fall, urination and nutrition, should be performed as part of the care of elderly diabetic patients, in particular old-old patients. Because geriatric syndromes are multifactorial and share risk factors, diabetic people with any geriatric symptoms should be treated with a common concentric strategy, such as supervised exercise therapy including muscle-strengthening training, psychological support, social support for adherence, and good glycemic control with avoidance of hypoglycemia.

Keywords: cognitive impairment, diabetes mellitus, disability, elderly, geriatric syndrome.

Introduction

Diabetes mellitus is more common in the elderly population. At least one-sixth of the elderly population has diabetes mellitus in Japan and other countries.[1,2] The treatment of diabetes mellitus in the elderly population, in particular the old-old people, is often difficult because of impairment of their physical, psychological and cognitive functions, and the lack or shortage of family or social support. Elderly diabetic patients may have increased risk for functional dependency and frailty. Therefore, a comprehensive geriatric assessment may be a necessity in the treatment of elderly patients.[3]

Another important approach to diabetes in the elderly is the assessment, prevention and treatment of geriatric syndrome. The so-called "geriatric syndrome" refers to multifactorial health conditions that occur when the accumulated effects on multiple systems render an old person vulnerable to situational changes.[4] Geriatric syndrome is related to the impairment of multiple systems due to aging as well as age-related disease. Diabetes mellitus is considered to lead to accelerated aging because of both the accumulation of advanced glycation end products, a marker of aging, in the tissues and the high incidence of atherosclerotic disease compared with non-diabetic populations. Also, because the development of diabetic micro- and macrovascular complications is dependent on the duration of diabetes, symptoms of the complications may be concentrated in the elderly. The diabetes population has a high prevalence of geriatric syndrome such as functional disabilities, depression, fall, urinary incontinence, pain and dementia, which occur due to the aging and diabetic complications. The geriatric symptoms lead to frailty, loss of independence and low quality of life. Importantly, these geriatric symptoms are major obstacles in the treatment and care of diabetic people.

In this article, we review geriatric symptoms in diabetes mellitus and discuss an approach to the assessment, prevention, and treatment of geriatric syndromes in diabetic people.

Accepted for publication 22 October 2008.

Correspondence: Dr Atsushi Araki MD PhD, Department of Endocrinology, Tokyo Metropolitan Geriatric Hospital, 35-2 Sakae-cho, Tokyo 173-0015, Japan. Email: aaraki@tmgh.metro.tokyo.jp

doi: 10.1111/j.1447-0594.2008.00495.x