≧140mmHg or 最小血圧値≧90mmHg or 服薬中)、高脂血症（血清トリグリセライド値≧150mg/dl（空腹時）；≧250mg/dl（随時）or HDLコレステロール値＜40mg/dl)、高血糖（血糖値≧110mg/dl or 服薬中)、喫煙、心房細動（ミネソタコード8-3)、心電図STT異常（ミネソタコード4/1～3 or 5/1～3)、眼底異常(Scheie分類H≧1 or S≧1)、多量飲酒(2合以上／日)、肥満（BMI≧25kg/m^2）を採り上げ、脳卒中、虚血性心疾患の発生に対する各リスクファクターの相対危険度をCox比例ハザードモデルによる多変量解析により、年齢を含む各因子の交絡作用を調整して算出した。また、メタボリックシンドローム（日本の基準、腹部肥満はBMI≧25kg/m^2で代用）の循環器疾患発生に対する相対危険度について、メタボリックシンドロームの基準に含まれる因子は除外し、年齢、喫煙、高コレステロール血症（血清総コレステロール値≧220mg/dl or 服薬中)、飲酒状況を調整して算出した。そして、得られた相対危険度をもとに、Rockhillらの方法(Am J Public Health 1998;88:15-19）により、集団寄与危険割合をもとめた。さらに、肥満の有無別、リスク（血圧高値、高脂血症、高血糖）の集積個数別に循環器疾患発生の相対危険度、集団寄与危険割合も同様に算出した。

本検討により得られた相対危険度は、地域間で多少の相違はあるものの大差はなかった。このため本成績は4地域を合算し、多変量解析にあたっては、地域も一変数として扱い、交絡因子として調整した。

（倫理面への配慮）本研究は、「疫学研究に関する倫理指針」ならびに個人情報保護に関する国のガイドラインや指針等に則ってデータ解析を行ない、大阪府立健康科学センター倫理審査委員会の承認を得た。

C．研究結果

追跡期間中に脳卒中は243例、虚血性心疾患は81例発生した。脳卒中のリスクファクターを表1に示す。脳卒中発生の相対危険度は、心房細動が3.1と最も高く、次いで有意の危険因子として、高血圧2.1、心電図STT異常2.2、眼底異常1.6、メタボリックシンドローム1.6であった。脳卒中発生への集団寄与危険割合は、高血圧の集団寄与危険割合が35%と最も高く、次いで眼底異常17%、多量飲酒11%であり、メタボリックシンドロームは7%であった。

脳卒中を病型別に分けて検討したところ（図1)、脳出血に対する相対危険度は、多量飲酒が3.3と最も大きく、次いで心電図STT異常、高血圧、眼底異常の相対危険度が2以上の値を示した。脳出血への集団寄与危険割合は、高血圧が40%と最も高く、次いで多量飲酒、眼底異常の寄与割合が高かった。脳梗塞については、心房細動の相対危険度が4.2と最も大きく、次いで心電図STT異常、高血圧、メタボリックシンドロームの相対危険度が2以上の値を示した。脳梗塞への集団寄与危険割合は、高血圧が33%と最も高く、他のリスクファクターの寄与割合は比較的小さかった。脳梗塞の中で最も多い病型である穿通枝系梗塞に対する相対危険度は、高血圧が3.1と断然高かった。穿通枝系梗塞への集団寄与危険割合も高血圧が51%と最も高く、次いで喫煙が24%であった。メタボリックシンドロームの集団寄与危険割合は脳梗塞で比較的高かったが、それでも11%と他のリスクファクターに比べると大きくはなかった。

虚血性心疾患発生に対する有意のリスクファクターの相対危険度は、高コレステロール

血症2.1、高脂血症1.8、喫煙1.6であり、メタボリックシンドロームは1.1であった（図2）。

また、虚血性心疾患への集団寄与危険割合は、喫煙が26%と最も高く、次いで高血圧と高コレステロール血症が17%、高脂血症が13%であった。虚血性心疾患発生に対するメタボリックシンドロームの集団寄与危険割合はわずか2%であった。

次に、肥満の有無別、リスク（高血圧、高脂血症、糖尿病）の集積個数別に循環器疾患発生のリスクを算出した結果（図3）、脳卒中、虚血性心疾患ともに、肥満の有無に関係なく、リスク個数が多くなるほど相対危険度は大きくなり、同じリスク個数区分でみると、いずれの相対危険度も肥満の有無で大差ないと考えられた。集団寄与危険割合は、脳卒中、虚血性心疾患ともに肥満が無くリスクを2個以上有する者の集団寄与危険割合が最も高く、次いで肥満が無くリスクを1個有する者の寄与割合が高かった。肥満が有りリスク個数が2個以上の者（メタボリックシンドローム）の集団寄与危険割合は、脳卒中で15%、虚血性心疾患で7%であった。

D．考察

今回対象とした地域住民の成績では、相対危険度ならびに集団寄与危険割合の両方を考慮すると、脳卒中については、高血圧が最大の危険因子であり、眼底異常と心電図STT異常も高血圧性臓器変化の指標として独立したリスクファクターであった。さらに脳出血については多量飲酒、脳梗塞については心房細動がそれぞれ相対危険度の高いリスクファクターであった。メタボリックシンドロームは、脳梗塞発生に対する相対危険度が比較的高かったものの、集団寄与危険割合は比較的小さかった。虚血性心疾患については、喫煙、高血圧、高コレステロール血症の古典的3大危険因子が依然として影響力が大きいことが示された。さらに肥満の有無に関係なく、リスクファクターの保有個数が多い者ほど脳卒中、虚血性心疾患のいずれの発生にもより多く関わっていることが明らかとなった。

以上より、今回の対象地域では、住民全体の循環器疾患発生を減少させるためには、肥満の有無にかかわらず高血圧対策を強力に推進し、同時に喫煙および高コレステロール血症に対する対策を実施していくことが効果的であると考えられた。特定健診・特定保健指導では、肥満基準による制約があるため、これらの個々の危険因子には十分対応できないため、追加的な取り組みが求められる。対策の方向性を誤ると十分な予防効果を上げられない可能性があることから、早急に予防対策の内容を再考する必要があると考える。

ただし、本成績が全国全ての地域に当てはまるかについては不明である。留意すべき点は、今回の対象地域はいずれも地域ぐるみで循環器疾患予防対策を熱心に継続して実施してきた地域であるため、そこに居住している住民の健康意識は周辺地域よりも高いと考えられる。このため生活習慣や健診成績も比較的良好である可能性がある。また、今回はあくまでも健診を受診した者のみのフォローアップ成績であるため、健診を受診していない循環器疾患発生者の身体状況はわからない。したがって、全国的にみると、メタボリックシンドロームの頻度がより高く、メタボリックシンドローム対策が有効である地域もあろう。時代とともに変貌しつつある循環器疾患の動向とその背景要因は、全国一様ではない

と考えられ、それぞれの地域での現状分析とその結果に基づいた対策が求められる。

E．結論

地域住民の疫学的追跡調査の結果、住民全体の循環器疾患発生を減少させるためには、肥満の有無にかかわらず高血圧対策を強力に推進し、同時に喫煙および高コレステロール血症に対する対策を推進していくことが効果的であると考えられた。

F．健康危険情報

なし

G．研究発表

1．論文発表

なし

2．学会発表

1）北村明彦．Trends in the Incidence of Coronary Heart Disease and Stroke and Their Risk Factors, the Akita-Osaka Study. 第41回日本動脈硬化学会総会シンポジウム（2009.7.17）．プログラム・抄録集 p.168.

2）北村明彦．大阪、秋田研究等からのエビデンスに基づく循環器病予防対策の実践と課題．第68回日本公衆衛生学会総会シンポジウム（2009.10.22）．日本公衛誌．2009;56(特別附録）:82.

3）北村明彦．Company and community-based preventive program for cardiovascular disease. 第74回日本循環器学会総会シンポジウム（2010.3.6）．Circulation J. 2010;74(supple Ⅰ);48.

H．知的財産権の出願・登録状況

なし

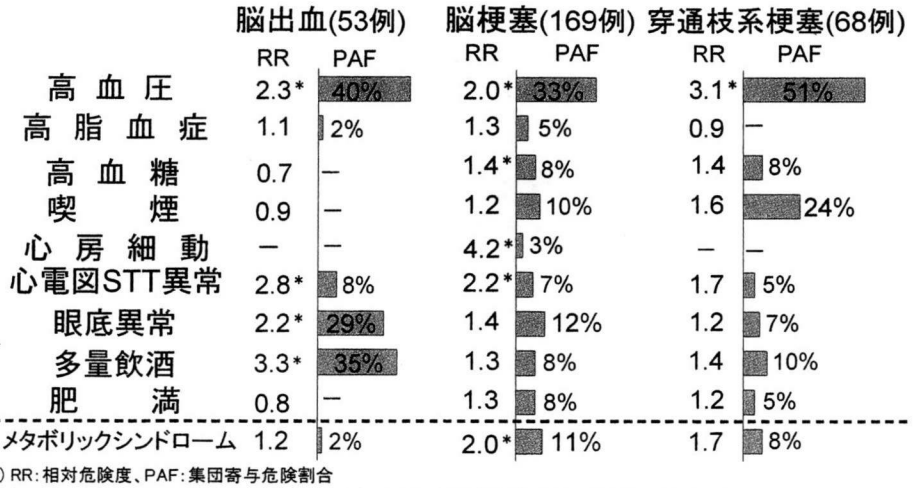
〔共同研究者〕　前田健次（大阪府立健康科学センター）

表1. 脳卒中のリスクファクター(男)

発症数243例	相対危険度	発生者中の割合	集団寄与危険割合
高 血 圧	2.1*	67%	35%
高 脂 血 症	1.1	20	2
高 血 糖	1.2	25	5
喫 煙	1.2	61	9
心 房 細 動	3.1*	3	2
心電図STT異常	2.2*	13	7
眼底異常	1.6*	47	17
多量飲酒	1.4	39	11
肥 満	1.2	30	4
メタボリックシンドローム	1.6*	19	7

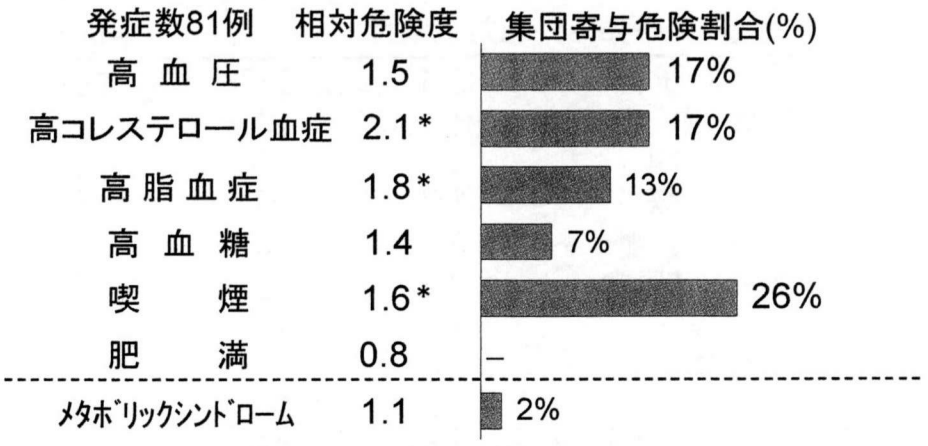
高 血 圧 :SBP≧140/DBP≧90/治療中 高脂血症 :TG≧150(空腹時)≧250(随時)/ HDLC＜40
高 血 糖 :GL≧110(空腹時)≧140(随時)/治療中 心電図STT異常:4-1～3 / 5-1～3 眼底異常:Scheie H≧1/S≧1
多量飲酒:2合以上／日 肥満:BMI≧25 メタボリックシンドローム:日本の基準(腹部肥満はBMI≧25で代用)

図1. 脳卒中の病型別リスクファクター(男)



注) RR:相対危険度、PAF:集団寄与危険割合
高 血 圧 :SBP≧140/DBP≧90/治療中 高脂血症 :TG≧150(空腹時)≧250(随時)/ HDLC＜40
高 血 糖 :GL≧110(空腹時)≧140(随時)/治療中 心電図STT異常:4-1～3 / 5-1～3 眼底異常:Scheie H≧1/S≧1
多量飲酒:2合以上／日 肥満:BMI≧25 メタボリックシンドローム:日本の基準(腹部肥満はBMI≧25で代用)

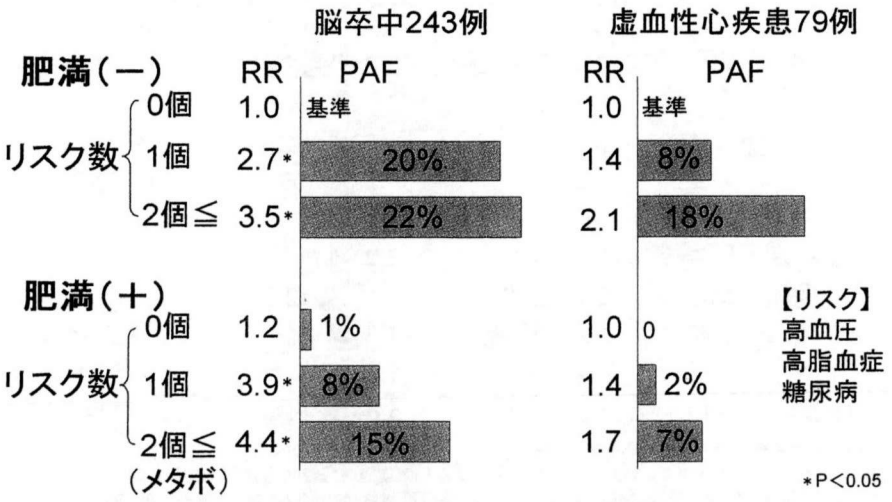
図2. 虚血性心疾患のリスクファクター(男)



高 血 圧 :SBP≧140/DBP≧90/治療中　高コレステロール血症:TCH ≧220/治療中
高脂血症 :TG≧150(空腹時)≧250(随時)/ HDLC＜40　高 血 糖 :GL≧110(空腹時)≧140(随時)/治療中
肥満:BMI≧25　メタボリックシンドローム:日本の基準(腹部肥満はBMI≧25で代用)

図3. 循環器疾患のリスクファクター(男)

－肥満の有無別、リスクの集積個数別検討－



注) RR:相対危険度、PAF:集団寄与危険割合

別紙４

研究成果の刊行に関する一覧表

大阪府立健康科学センター　北村明彦

書籍、雑誌ともに無し

厚生労働科学研究費補助金(循環器疾患等生活習慣病対策総合研究事業)
分担研究報告書

沖縄県における心臓血管イベント発症要因の解明(沖縄豊見城研究)

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研究要旨:研究要旨:沖縄県の人間ドック受診者において、生活習慣病関連の危険因子を調査した。内臓肥満症、高血圧、耐糖能異常、脂質異常症のいずれも全国平均より高いことがわかった。急性心筋梗塞の発症率は、男性 2.01、女性 1.03(千人年)、冠動脈疾患(急性心筋梗塞＋労作性狭心症)男性3.40、女性2.06(千人年)、脳卒中3.47、女性2.49(千人年)であった。腹部肥満、高血圧、高血糖、高中性脂肪、低HDL血症の陽性率、喫煙率、習慣飲酒率でも、男性が女性に比較して高く、高コレステロール血症は男女で有病率に差がなかった。心血管イベントの発生率には男女差があり、その発生要因も明らかな差がある。本年度は、心臓血管イベントのリスクのひとつである高尿酸血症の心血管イベントの発生率に及ぼす影響について調査を開始した。まず、高尿酸血症と血管内皮機能の関係を内臓肥満症およびインスリン抵抗性との関連から検討した。人間ドックで2次健診を勧奨された540名(男性355名、女性185名)を対象。対象症例の尿酸値は、男性 6.48 ± 1.37 mg/dL(平均±標準偏差、95%信頼区間 6.34 - 6.63)、女性5.07 ± 1.52 mg/dL(4.83 - 5.32)であった。高尿酸血症自体は、マルチプリリスク・コンポーネントとして、血管機能異常の予測能を高めることが確認された。一方、直接血管機能に影響する証拠は不十分であり、基礎的および実験的臨床研究の結果を含め、今後慎重に検証する必要があると考える。

A. 研究目的

沖縄県における心臓血管イベント発症要因を解明する。メタボリックシンドロームのコンポーネントを含めた動脈硬化性疾患リスクファクターの陽性率と心血管イベントの発生率との関係を明らかにする。

B. 研究方法

研究1: 2003年5月から2004年3月まで豊見城中央病院健康管理センターを人間ドックのため受診した者6985名(年齢30～69才、男性3839名、女性3146名)。メタボリックシンドロームの各コンポーネントの陽性率と他の動脈硬化危険因子の陽性率を調査する。研究2:研究1で対象となった症例につき、毎年の受診歴をカルテ上で確認し、受診歴の不明なものに対して、往復はがきで健康状態、死別の有無に関する調査を行う。メタボリックシンドローム診断基準は注1に示す通り。メタボリックシンドロームに対して、食事療法、運動療法、薬物療法の有無を調査し、プライマリーエンドポイントおよびセカンダリーエンドポイントを判定する。研究 3:人間ドックで2次健診を勧奨された540名(男性355名、女性185名)を対象として以下の検討をおこなった。尿酸を含めた糖脂質代謝パラメータ、血管機能指標として、前腕動脈の反応性充血時血管内径拡張率(FMD:flow-mediated dilatation)、ニトログリセリン反応性血管内径拡張率(NMD::nitroglycerin-mediated dilatation)および尿中微量アルブミン(UAE mg/Cr·g)を測定した。

(倫理面への配慮)
ヘルシンキ宣言(http://www.wma.net/e/policy/b3.htm)を遵守している。予後問い合わせのはがきでは、調査に関する情報保護シールを貼ることで、また、統計解析ならびに中央の疫学解析委員会におけるデータ提供の際は、連結不可匿名化をおこない個人が特定されない処理を厳重におこない、個人情報の遺漏がないことに徹底して留意した。

C. 研究結果

研究1および2:対象とした者人間ドック受診者6985名のメリスクファクターの頻度は以下の

通りである。腹部肥満陽性率は、男性58%(≥85cm)31%(≥90cm)、女性53% (≥80cm)17%(≥90cm)。空腹時高血糖または血糖降下薬内服の率は、男性53%(≥100mg/dl)、21%(≥110)、女性24%(≥100)、8%(≥110)であった。総これてすロール血症(≥220mg/dlまたは内服中)は男性32%、女性33%、高中性脂肪血症(≥150または脂質異常症治療薬内服)は、男性41%、女性18%であった。低HDL血症(<40または脂質異常症治療薬内服)の有病率は、男性20%、女性11%(<50だと25%)であった。高血圧症(≥130/85mmHgまたは内服)の有病率は、男性55%、女性38%であった。メタボリックシンドロームの陽性率は男性は、27%(日本基準_腹囲85cm)23%(IDF_腹囲90cm)、14%(AHA/NHLBI_2005年改訂_腹囲90cm)であった。。女性は、6%(日本基準_腹囲90cm)24%(IDF_腹囲80cm)、24%(AHA/NHLBI_2005年改訂_腹囲80cm)であった。喫煙率(男性喫煙中34%+既往喫煙25%、女性喫煙中5%+既往喫煙2%)、習慣飲酒率(週1回以上、男性81%、女性31%)であった。

平均観察期間(男性1346日、女性1358日)で、初発心筋梗塞(男性21例、女性12例)、初発労作性狭心症(男性227例、女性12例)、初回冠動脈インターベンション(男性221例、女性6例)、初発脳卒中(男性49例、女性29例)、急性死(男女とも0例)、死亡(男性4例、女性0例)であった。 急性心筋梗塞の発症率は、男性2.01、女性1.03(千人年)、冠動脈疾患(急性心筋梗塞+労作性狭心症)男性3.40、女性2.06(千人年)、脳卒中3.47、女性2.49(千人年)であった。内服薬服用率は、降圧薬(男性17%、女性16%)、脂質異常症治療薬(男性6%、女性7%)、糖尿病治療薬(男性5%、女性2%)であった。

研究3:人間ドックで2次健診を勧奨された540名(男性355名、女性185名)を対象。対象症例の尿酸値は、男性 6.48 ± 1.37 mg/dL(平均±標準偏差、95%信頼区間 6.34 - 6.63)、女性5.07 ± 1.52 mg/dL(4.83 - 5.32)であった。HOMA-IR4分位でみると高値群で尿酸値が高かったが(P=0.008)、VFA4分位でみると尿酸値に差はなかった。尿酸値と血管機能指標(FMD、NMDおよびUAE)に相関関係はなかった。対象者を尿酸レベルで4分位あるいはインスリン抵抗性指数(HOMA-IR)レベルで4分位にわけても、FMD、NMDおよびUAEの群間差はなかった。一方内臓脂肪面積(VFAcm2)レベルで4分位にわけると、FMD、NMDで群間差はなかったが、VFA高値群でUAEが高値であった。さらに、メタボリックシンドロームのコンポーネントに高尿酸血症の有無を加えたとき、FMDおよびUAE異常を検出する予測能が高まった。

D. 考察

メタボリックシンドロームのコンポーネントを含めた動脈硬化性疾患リスクファクターの陽性率と心血管イベントの発生を全件調査した。 平均観察期間男性1346日、女性1358日で、急性心筋梗塞の発症率は、男性2.01、女性1.03(千人年)、冠動脈疾患(急性心筋梗塞+労作性狭心症)男性3.40、女性2.06(千人年)、脳卒中3.47、女性2.49(千人年)といずれも男性が女性に比較して、高率であった。

一方で、腹部肥満、高血圧、高血糖、高中性脂肪、低HDL血症の陽性率、喫煙率、習慣飲酒率でも、男性が女性に比較して高く、高コレステロール血症は男女で有病率に差がなかった。

高尿酸血症は、内臓肥満症およびインスリン抵抗性を基盤とするメタボリックシンドロームに合併することが多く、血清尿酸値は心血管イベントの予測マーカーとなる可能性がある。複数の前向き試験の結果から、血清尿酸値が心血管イベントの単なる予測マーカーではなく、発症メカニズムにも関与する可能性が指摘されている。さらに血管局所で尿酸トランスポーターが発現していることから、高尿酸血症と血管機能との関連にも注目が集まっている。本研究では高尿酸血症と血管内皮機能の関係を内臓肥満症およびインスリン抵抗性との関連から検討した。これらの検討の結果、高尿酸血症は、内臓肥満症およびインスリン抵抗性と密接に関係していることを明らかにした。高尿酸血症自体は、マルチプリリスク・コンポーネントとして、血管機能異常の予測能を高めることが確認された。一方、直接血管機能に影響する証拠は不十分であり、基礎的および実験的臨床研究の結果を含め、今後慎重に検証する必要があると考える。

E. 結論

心血管イベントの発生率には男女差があり、その発生要因も明らかな差がある。メタボリックシンドロームの診断・管理のためには、男女差を考慮にいれて個別のアプローチ基準を設定する必要があると考えられた。さまざまリスクひとつずつにつき、その病態における関与、マーカーとしての有用性につき慎重に検討を進める必要がある。

F. 健康危険情報
(総括研究報告書にまとめて記入)

G. 研究発表
1. 論文発表
別紙4参照
2. 学会発表
(発表誌名巻号・頁・発行年等も記入)

G. 研究発表

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H. 知的財産権の出願・登録状況

1. 特許取得

なし

2. 実用新案登録

なし

3. その他

なし

別紙4

研究成果の刊行に関する一覧表

書籍 なし。

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Okuno Y, Matsuda M, Miyata Y, Fukuhara A, Komuro R, Shimabukuro M, Shimomura I.	Human Catalase Gene is Regulated by Peroxisome Proliferator Activated Receptor-gamma through a Response Element Distinct from That of Mouse.	Endocr J.	in press	in press	2010

別紙３

研究報告書

厚生労働科学研究費補助金（循環器疾患等生活習慣病対策総合研究事業）
分担研究報告書

血圧に関する診断のエビデンスに関する研究

研究分担者　伊藤貞嘉　東北大学大学院医学系研究科内科病態学講座教授

研究要旨Advanced glycation end products(AGEs)の前駆物質であるMethylglyoxal(MG)が糖尿病の血管障害および高血圧進展に関与する独立因子であることを明らかにするため、２型糖尿病50例においてMGを測定し、MGとその後５年間の頚動脈内膜中膜複合体肥厚(IMT)と血圧上昇との関連を検討した。その結果MGはIMTや血圧変化の独立した危険因子であった。

A．研究目的

MGが糖尿病における血管障害および高血圧進展の独立した危険因子であることを明らかにする。

B．研究方法

2型糖尿病例を対象としたclinical prospective observation study。50名の対象のMGを測定し、その後5年間のIMTの変化、血圧の変化、糸球体ろ過率(eGFR)の変化、尿アルブミン排泄量(ACR)の変化との関連を重回帰分析にて評価した。

（倫理面への配慮）

本研究は介入研究ではなく観察研究であり、対象は本来受けられる治療の妨げになることはない。個人情報保護のため連結困難な匿名化を行っている。本研究は東北大学倫理委員会の承認を受けている。充分なｲﾝﾌｫｰﾑﾄﾞｺﾝｾﾝﾄを行い同意取得の上で行われた。

C．研究結果

MGと測定時点の肥満(BMI)、血圧、eGFR、中性脂肪(TG)と相関した。単回帰分析では、MGは5年間のIMTの変化、血圧の変化、eGFRの変化、ACRの変化と相関を示した。ところが重回帰分析ではMGはIMTの変化、血圧の変化の独立した危険因子であったが、eGFRの変化、ACR変化の危険因子ではなかった。

D．考察

MGが長期に渡る（5年）の糖尿病性血管症進展や血圧上昇を起こす可能性が示唆された。糖尿病腎症進展にはMG以外の別の因子も関与する可能性が考えられた。今後MG（もしくはAGEs）の形成を抑制する治療によりこれらの血管障害進展が抑制されるかどうかの確認が必要である。

E．結論

糖尿病におけるMGの増大は5年後の血管障害、血圧上昇の危険因子である。

G．研究発表

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H．知的財産権の出願・登録状況
（予定を含む。）

1. 特許取得
なし
2. 実用新案登録
なし
3. その他
なし

別紙４

研究成果の刊行に関する一覧表レイアウト（参考）

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伊藤貞嘉	腎疾患の最近の動向	金澤一郎、永井良三総編集	今日の診断指針第6版	医学書院	東京	2010	1022

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Ito S	Controversies on Obesity and CKD	Circulation Journal	74	428-429	2010

Circulation Journal
Official Journal of the Japanese Circulation Society
http://www.j-circ.or.jp

EDITORIAL

Controversies on Obesity and CKD

Sadayoshi Ito, MD

The metabolic syndrome (MetS) and chronic kidney disease (CKD) are two major worldwide public health problems. MetS is a cluster of risk factors for cardiovascular disease and type 2 diabetes mellitus, and the risk factors include dysglycemia, raised blood pressure, elevated plasma triglyceride levels, low high-density lipoprotein cholesterol levels and obesity (particularly abdominal obesity). There have been considerable disagreements over the diagnostic criteria of MetS, particularly regarding the requirement of obesity for the diagnosis. Of note, the International Diabetes Federation and the American Heart Association/ National Heart, Lung, and Blood Institute have recently agreed that abdominal obesity should not be a prerequisite for diagnosis but that it is 1 of 5 criteria, so that the presence of 3 of 5 risk factors constitutes a diagnosis of MetS.[1]

Article p462

CKD is another important public health concern. CKD is defined as the presence of reduced GFR (less than 60 ml·min^{-1}·1.73 m^{-2}) and/or evidence of renal damage (such as proteinuria) for more than 3 months. Epidemiological studies have now established that CKD is not only a significant risk for end-stage renal disease (ESRD) but also is associated significantly with high cardiovascular morbidity and mortality.

There is an epidemic of obesity and MetS across the world. In parallel, the number of CKD patients has been increasing over the last decade and is expected to grow even further. The most important established risk factors for CKD are diabetes mellitus and hypertension.[2] In addition, population-based, cross-sectional studies and prospective observational cohort studies have shown that obesity and MetS are predictors of CKD and ESRD.[3] Even in non-diabetic and no-hypertensive subjects, MetS has been shown to be independently associated with CKD.[4-6] However, the relationship between MetS and CKD has not been well studied in clinical settings.

In this issue of the Journal, Liu et al reported that the prevalence of MetS and CKD (defined as GFR less than 60 ml·min^{-1}·1.73 m^{-2} regardless of the presence or absence of other signs of renal injury) was 53.0% and 21.1%, respectively, in 3,465 Chinese patients admitted to cardiovascular wards with coronary artery disease (CAD).[7] Patients with MetS had a higher prevalence of CKD than those without MetS (22.7% vs 19.2%). All components of MetS, except central obesity, were significantly associated CKD, and the CKD prevalence became progressively higher as the number of MetS components increased. In addition, in subjects with 3 or 4 MetS components other than central obesity, the presence of obesity did not increase the prevalence of CKD. Thus, a multivariate-adjusted model suggested that the inclusion of abdominal obesity as a prerequisite for MetS diagnosis diluted the impact of MetS on CKD in this population with CAD. While the diluting effect of obesity is interesting to note, the interpretation of the results needs careful attention, especially in relation to the phenomenon of reverse-epidemiology. Because CKD is a significant risk factor even in the absence of obesity, it is likely that the study population included many CKD patients with classical risk factors (hypertension, dyslipidemia and/or dysglycemia) but without obesity.

The prevalence of MetS in Asian population is reported to be 10–25%, while that of CKD is about 10% in general population.[4,8-10] The substantially higher prevalence of MetS and CKD in the Liu's study than that reported in general populations is consistent with previous findings, endorsing that MetS and CKD are both significant risk factors for CAD.

In general, population-based cross-sectional studies have reported that MetS is significantly associated with CKD and that the prevalence of CKD becomes higher as the number of MetS' components increases.[8-10] However, the association between MetS and CKD may depend on various factors including gender, age and co-morbid conditions. Yu et al reported that the prevalence of CKD was significantly higher in the MetS group as compared with the non-MetS group (13.7% vs 4.7%). However, sub-group analysis revealed that the prevalence of CKD in men was higher in the presence of MetS only under the age of 60, whereas in women the CKD prevalence in MetS group became significantly higher only after the age of 50. The subjects of the Liu's study had CAD, and the study included many elderly patients (67 years old on average), more men (77%) than women and many patients with hypertension (71%) and diabetes (42%).[7] These characteristics of the study population may explain a relatively weak association between MetS and CKD.

It is unclear whether obesity is a risk factor of CKD, independent of hypertension and diabetes. Studies have shown that increased body mass index (BMI) may be associated with elevated risks of CKD and ESRD.[2,10,11] However, other studies have found no such correlations. Framingham Offspring participants (n=2,676) free of CKD at baseline were

Received January 19, 2010; accepted January 19, 2010; released online February 9, 2010
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ISSN-1346-9843 doi:10.1253/circj.CJ-10-0046

followed up for 18.5 years, and it was found that obesity was associated with increased risk of developing CKD (odd ratio; 1.68).[12] However, after adjustment for known cardiovascular risk factors, there was no longer a significant association. In a prospective five-year follow-up study involving 6,371 subjects without diabetes or proteinuria at baseline, Tozawa et al reported that MetS was a predictor of development of proteinuria but not reduced GFR.[13]

There is a constellation of pathognomonic renal lesions associated with morbid obesity, and this entity is called obesity-related glomerulopathy.[14] Focal segmental glomerulosclerosis (FGS) is the most significant and frequent histological abnormality in proteinuric morbidly obese patients. Although patients with obesity-related glomerulopathy usually exhibit less severe proteinuria as compared those with "idiopathic" FGS, the long-term prognosis of the former is poor, with almost one-half ultimately developing advanced renal failure. There has been a rise in the incidence of obesity-related glomerulopathy in the past 2 decades, which seems to be congruent with the sharp increase in the prevalence of obesity. However, detailed information, such as the prevalence, clinical courses and effective therapeutic modalities, is not available at present.

Obesity is one of the important components of MetS, and it is thought to play a central role in the pathogenesis of MetS. However, there is uncertainty as to whether obesity itself is causally related to development of CKD. In addition, the impact of obesity on CKD and its clinical significance may be different according to the gender, age, stage of CKD and co-morbid conditions. Furthermore, it is well established that hypertension, diabetes and dyslipidemia are significant risk factors for cardiovascular diseases and CKD even in the absence of obesity. Therefore, estimating the level of risk only using the criteria that require obesity as an absolute prerequisite may cause erroneous failure in identifying the subjects at the risk of cardiovascular disease and/or CKD.

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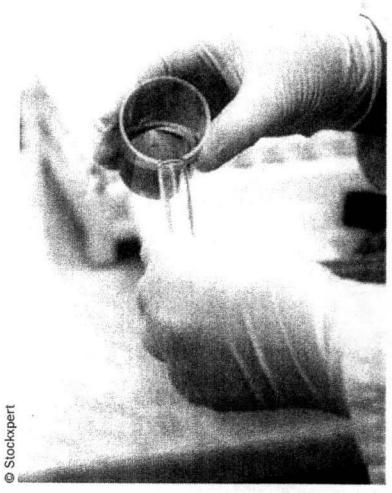
PROTEINURIA

Usefulness of RAS inhibition depends on baseline albuminuria

Sadayoshi Ito

In patients at low risk of renal disease and with low levels of albuminuria, administration of renin–angiotensin system inhibitors does not seem to offer renal benefits and might cause adverse renal effects. In these patients, renin–angiotensin system inhibition should be implemented judiciously, with doses titrated to individual needs and with careful monitoring of kidney function.



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Inhibitors of the renin–angiotensin system (RAS) have been shown to blunt progression of advanced kidney disease. However, the long-term renal effects of these therapeutic agents in patients with moderate or no renal disease are not clear. The availability of such information is important because RAS inhibitors are widely used, particularly in patients at high cardiovascular risk. On this background, the report by Mann and colleagues of the renal outcomes of the Telmisartan Randomised Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease (TRASCEND) suggests that administration of telmisartan has little or no renal benefit for patients at high risk of cardiovascular events but without macroalbuminuria.[1]

In TRANSCEND, patients with cardiovascular disease or diabetes but without macroalbuminuria or heart failure who could not tolerate angiotensin-converting-enzyme inhibitors were randomly assigned to receive the angiotensin receptor blocker telmisartan (80 mg daily) or placebo and were followed for an average of 56 months. Although microalbuminuria developed less frequently in the telmisartan group than in the placebo group, doubling of serum creatinine was seen more frequently in the treatment group. Only a few patients in either group required dialysis and changes in estimated glomerular filtration rate (eGFR) were not associated with subsequent death or composite outcome of myocardial infarction, stroke and cardiovascular death.

RAS inhibitors have been shown to reduce proteinuria and the rate of loss of renal function in patients with chronic kidney disease.[2–5] However, the benefits of RAS inhibition seem to depend on the degree of proteinuria at baseline.[6] Namely, RAS inhibition has been shown to be beneficial in patients with at least 0.5 g per day proteinuria, whereas no convincing evidence exists to demonstrate the benefits extend to patients with a lower level of proteinuria. A subgroup analysis of TRANSCEND showed that telmisartan treatment was associated with an increased risk of adverse renal events in patients with normal albuminuria, whereas it tended to improve outcomes in patients with microalbuminuria. Albuminuria level is, therefore, an important consideration when selecting patients for treatment with RAS inhibitors. In addition, previous studies have reported a close association of not only baseline proteinuria but also of changes in albuminuria during study follow-up with cardiovascular and renal outcomes.[7–9] Whether an association between albuminuria changes and study outcomes also exists in TRANSCEND participants would be interesting to know.

In participants of TRASCEND, eGFR was fairly stable and the average rate at which it decreased was lower than 1 ml/min per year. However, eGFR decreased more quickly in patients on telmisartan than in those on placebo, although the change itself was small. The decrease in eGFR was mainly observed during initial 6 weeks of the trial, with a slight decline occurring thereafter only in the telmisartan group. A larger decline in eGFR from baseline to 6 weeks and from baseline to 2 years was associated with a lower increase in urinary albumin to creatinine ratio (UACR) from baseline to 2 years. Furthermore, decreased eGFR was associated with decreased systolic blood pressure. These findings suggest that changes in renal hemodynamics are primarily responsible for changes in both eGFR and UACR. Although changes in eGFR were not associated with cardiovascular events or death, Mann *et al.* do not report whether these changes were related to the risk of doubling of serum creatinine, which would be a clinically relevant finding. In general, the factors associated with the risk of doubling of serum creatinine in the telmisartan group would be important to clarify.

Notably, the composite outcome of dialysis or doubling of serum creatinine occurred mainly in patients with normal renal function (eGFR >60 ml/min/1.73 m^2) and without microalbuminuria. This observation might be explained by the complex interplay among RAS, salt balance and renal function. From an evolutionary point of view, land-dwelling organisms have had to adapt to an environment where access to salt and water is generally difficult and the risk of wound injuries high.[10] Hypotension and hypoperfusion of vital organs were, therefore, the principal challenges with which these organisms had to cope with, and the potent vasoconstricting and sodium-retaining effects of RAS were an indispensable adaptive tool. Inhibition of RAS might increase the risk of hypotension and acute kidney injury in individuals who undergo major surgery and in those with conditions such as acute illness, dehydration or sodium depletion (for instance caused by excessive use of diuretics). These renal risks might be particularly acute in normotensive individuals with normal renal function in whom the RAS responds to changes in sodium balance to maintain circulatory homeostasis with great sensitivity.

In TRANSCEND participants at high cardiovascular risk—who might also have had unrecognized intrarenal vascular lesions—repeated subtle renal insults, even if partially reversible, might have resulted in doubling of the level of serum

creatinine. In this regard, knowing whether the initial declines in eGFR, which were probably functional, were associated with the risk of doubling of serum creatinine would be important. In patients with microalbuminuria or reduced renal function, blood pressure is salt-sensitive and body-fluid volume is expanded under conditions of regular sodium intake. In these individuals, the RAS is less responsive to changes in sodium balance than in patients with normal renal function. As a consequence, fewer adverse renal events would be expected in association with RAS inhibition. Furthermore, the physicians of patients with a pre-existing renal condition would be particularly alert and responsive to possible adverse renal effects associated with this therapeutic approach.

The known benefits of RAS inhibition should be viewed in the context of the risk of potential adverse effects. In patients with chronic kidney disease, reducing albuminuria remains an important strategy for renal and cardiovascular protection. However, for patients at low renal risk and with low levels of albuminuria, RAS inhibition might not offer any renal benefit. RAS inhibitors should be used sparingly in these patients, doses should be titrated to individual needs and kidney function should be monitored closely. Although the organ-protecting effects of RAS inhibitors are thought to be independent of their effects on blood pressure, physicians should keep in mind that the RAS has a critically important role in maintaining homeostasis of body fluid volume and blood pressure.

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doi:10.1038/nrneph.2009.203

Competing interests
The author declares no competing interests.

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CHRONIC KIDNEY DISEASE

Is angiotensin system blockade indicated in the elderly?

Carolyn Bauer, Matthew Abramowitz and Thomas H. Hostetter

Evidence supporting the renal benefits of angiotensin-converting-enzyme inhibitors and angiotensin II receptor blockers in elderly patients without proteinuria is lacking. However, until such data are available, if tolerated, these medications should continue to be used in this patient population because of their potent effect on blood pressure.

The prevalence of chronic kidney disease (CKD) is increasing, and, in countries such as the US, the largest increase is observed among patients over 70 years of age.[1] The guidelines of several societies recommend using angiotensin-converting-enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) in patients with CKD, because of the strong evidence that treatment with these agents slows the progression of kidney disease.[2,3] O'Hare and colleagues have examined the utility of these guidelines in individuals over 70 years of age.[4] The researchers found that elderly patients were under-represented in the randomized, controlled trials used to create the guidelines. They also found that the trials that demonstrated renoprotection by ACE inhibitors and ARBs enrolled mostly patients with substantial proteinuria, a condition often not present in elderly patients with CKD.

Since many institutions and even governments have started requiring that estimated glomerular filtration rates (eGFRs) be reported along with serum creatinine measurements, many elderly individuals have been diagnosed with CKD. However, the clinical relevance of a mildly reduced eGFR in an elderly patient without proteinuria remains unclear. The Modification of Diet in Renal Disease equation that is used to diagnose CKD has yet to be validated in elderly individuals.[5] Evidence also suggests that elderly patients might progress to end-stage renal disease (ESRD) less rapidly than young patients.[6] The clinical course of elderly patients with CKD stages 3 and 4 is different from that of their young counterparts; elderly patients are significantly more likely to develop cardiovascular disease and die than progress to ESRD.[6] An overestimate of disease burden, a decreased risk of renal progression and an increased incidence of death would decrease the magnitude of the renal protection provided by ACE inhibitors and ARBs in elderly patients.

The renal benefits of ACE inhibitors and ARBs in proteinuric diseases are probably similar in elderly and in young patients. As O'Hare *et al.* point out, the majority of the studies cited in guidelines were conducted in patients with substantial proteinuria.[4] A *post hoc* analysis of the RENAAL trial showed that administration of an ARB to elderly patients with proteinuria reduced the risk of ERSD by half.[7] However, O'Hare *et al.* also demonstrate that proteinuria in elderly patients with an eGFR lower than 60 ml/min/1.73 m^2 is far less common than in their younger counterparts.[4] Thus the renal benefits of ACE inhibitors and

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SHORT REPORT

Angiotensin II Type 1 Receptor Blockers Reduce Urinary Angiotensinogen Excretion and the Levels of Urinary Markers of Oxidative Stress and Inflammation in Patients with Type 2 Diabetic Nephropathy

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Abstract

Objective: To demonstrate that the administration of an angiotensin (Ang) II type 1 receptor (AT1R) blocker (ARB) inhibits the vicious cycle of high glucose (HG)-reactive oxygen species (ROS)-angiotensinogen (AGT)-Ang II-AT1R-ROS by suppressing ROSs and inflammation, thus ameliorating diabetic nephropathy (DN).

Research Design and Methods: Thirteen hypertensive DN patients were administered ARBs, and the following parameters were evaluated before and 16 weeks after the treatment: urinary AGT (UAGT), albumin (albumin-creatinine ratio: ACR), 8-hydroxydeoxyguanosine (8-OHdG), 8-epi-prostaglandin F2α (8-epi-PGF2α), monocyte chemoattractant protein (MCP)-1, interleukin (IL)-6, and IL-10.

Results: ARB treatment reduced the blood pressure and urinary levels of AGT, ACR, 8-OHdG, 8-epi-PGF2α, MCP-1, and IL-6 but increased the urinary levels of IL-10. The reduction rate of UAGT correlated with the reduction rate of blood pressure; the reduction rates of the urinary ACR, 8-OHdG, 8-epi-PGF2α, MCP-1, and IL-6 levels; and the increase rate of the urinary IL-10 levels. Moreover, subjects who had high UAGT values at baseline exhibited higher reduction rates of urinary albumin excretion.

Conclusions: ARB-induced blockade of the abovementioned vicious cycle contributes to the renoprotective effects of ARBs in DN. The urinary levels of AGT could represent a predictive factor for reduced ACR in patients receiving ARB treatment.

Keywords: angiotensin II type 1, receptor blockers, diabetic nephropathy

Biomarker Insights 2009:4 97–102

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Introduction

High glucose (HG) levels lead to increased angiotensin (Ang) II generation in the kidney. Reactive oxygen species (ROSs) mediate a process that increases the levels of angiotensinogen (AGT), leading to increased Ang II generation.[1–3] HG induces AGT generation via the ROS–AGT pathway.[4–6] AGT generation mediated by HG-induced ROSs, accompanied by increased local production of Ang II, causes many pathophysiological changes associated with diabetic nephropathy (DN).[7–9] Ang II induces a further increase in the intracellular ROS levels via the activation of the Ang II type 1 receptor (AT1R).[10–11] Increased ROS levels, whatever they may be attributed to, cause inflammation and renal damage. Monocyte chemoattractant protein (MCP)-1 and interleukin (IL)-6 are assumed to be the key inflammatory factors involved in these effects. The renoprotective action of an AT1R blocker (ARB) is strongly related to its ROS-lowering effects.[10] In DN, the generation of ROS, AGT, and Ang II seems to increase remarkably when the vicious cycle of HG-ROS-AGT-Ang II-AT1R-ROS is activated.[1–9]

An ARB is expected to block this vicious cycle and thus decrease the urinary levels of inflammatory markers, ROS markers, albumin (measured as the albumin-creatinine ratio [ACR]), and AGT. Furthermore, all such effects of an ARB are expected to be closely correlated. However, these effects have not yet been clinically investigated. The present study was designed to confirm that AT1R blockade reduces the urinary AGT (UAGT) levels and to determine whether changes in these levels are closely related to changes in the ACR and in the levels of urinary ROSs and inflammatory markers. We therefore determined the ACR and the levels of UAGT, inflammatory markers, and ROSs before and after the administration of ARB to DN patients.

Research Design and Methods

The subjects enrolled in the present study were outpatients with hypertensive type 2 DN at our hospital. The enrollment criteria were as follows: mild to moderate hypertension (office systolic blood pressure (SBP) = 130–199 and/or diastolic blood pressure (DBP) = 70–110 mmHg), no use of antihypertensive agents such as RAS inhibitors, HbA_{1c} levels < 8%, ACR > 30 μg/mg Cre, and absence of hematuria. The present study was conducted after we obtained informed consent from all the subjects, and the study protocol was approved by the ethics committees of Tohoku University Hospital. Although 20 patients were initially enrolled, 7 were subsequently excluded for various reasons. Thus, the study finally involved 13 patients (7 men and 6 women) who had had diabetes for 13.4 ± 3.7 years. The subjects were administered ARBs (olmesartan in the case of 7 patients and valsartan in the case of 6). The following parameters were measured before and 16 weeks after the treatment: UAGT; oxidative stress markers such as 8-epi-prostaglandin F2α (8-epi-PGF2α) and 8-hydroxydeoxyguanosine (OHdG); the inflammatory markers MCP-1, IL-6, and IL-10; and the ACR.[10] The UAGT levels were determined using a newly developed ELISA.[12–14] The ACR and the levels of UAGT, 8-epi-PGF2α, 8-OHdG, MCP-1, IL-6, and IL-10 were expressed in terms of the median (range), because these factors did not exhibit normal distribution. The difference between the values determined before and after the treatment was analyzed using the Wilcoxon signed-rank test. All the other data were expressed as the mean ± standard error of the mean (SEM) and were statistically analyzed using the paired Student *t* test. Correlations were determined using the Spearman rank correlation test. $p < 0.05$ was considered significant.

Results

The changes in the clinical parameters evaluated before and after ARB administration were as follows: body mass index (kg/m^2), from 22.4 ± 0.7 to 22.5 ± 0.6 (not significant, $p = 0.8994$); HbA_{1c} (%), from 6.6 ± 0.3 to 6.6 ± 0.2 (not significant, $p = 0.9804$); SBP (mmHg), from 161.6 ± 2.8 to 145.7 ± 3.1 (–9.7% ± 2.2%, $p < 0.01$); DBP (mmHg), from 80.8 ± 1.8 to 78.6 ± 1.9 (–2.2% ± 2.3%, $p < 0.01$); serum creatinine (mg/dl), from 1.1 ± 0.1 to 1.3 ± 0.1 ($p < 0.05$); and K^+ (mEq/l), from 5.0 ± 0.2 to 5.3 ± 0.2 ($p < 0.05$). The ACR and the urinary levels of AGT, 8-epi-PGF2α, 8-OHdG, MCP-1, and IL-6 were significantly reduced (Table 1). However, the plasma levels of these markers remained unchanged (data not shown). The percent changes in the parameters evaluated before and after ARB administration are shown in Table 1. The reduction rate of the UAGT levels correlated with the reduction rates of the ACR ($y = 0.963x - 10.948$, $r = 0.7290$, $p < 0.001$;

Table 1. Urinary parameters evaluated before and 16 weeks after the administration of ARBs.

Parameters	Unit	Before	After	p	% Change
AGT	mg/g Cre	12.0 (3.7–39.9)	8.9 (2.5–29.8)	<0.05	−15.6 ± 5.8
albumin	mg/g Cre	2026 (894–3428)	1232 (548–3783)	<0.01	−25.9 ± 7.7
8-epi-PGF2α	ng/g Cre	247 (124–802)	207 (113–454)	<0.05	−10.4 ± 10.7
8-OHdG	μg/g Cre	8.7 (4.3–17.5)	5.4 (4.4–14.8)	<0.01	−21.7 ± 8.4
MCP-1	ng/g Cre	575 (51–2170)	652 (37–2620)	<0.05	−25.4 ± 9.4
IL-6	ng/g Cre	9.7 (0.2–36.5)	0.8 (0.2–38.5)	<0.01	−36.3 ± 21.8
IL-10	ng/g Cre	0.8 (0.3–2.8)	0.9 (0.3–6.3)	<0.01	50.0 ± 18.7

Notes: The parameters are expressed in term of the median (range). The percent change in the values determined after ARB administration as compared to those before administration is expressed as the mean ± SEM.
Abbreviations: AGT, angiotensinogen; 8-epi-PGF2α, 8-epi-prostaglandin F2α; 8-OHdG, 8-hydroxydeoxyguanosine; MCP, monocyte chemoattractant protein; Cre, urinary creatinine; IL, interleukin.

Fig. 1A) and the SBP ($y = 0.3103x - 4.8051$, $r = 0.8460$, $p < 0.001$, Fig. 1B); the reduction rates of the 8-OHdG ($y = 0.9488x - 6.9257$, $r = 0.6551$, $p < 0.01$; Fig. 1C), 8-epi-PGF2α ($y = 0.6584x - 0.1335$, $r = 0.3561$, $p < 0.01$; Fig. 1D), MCP-1 ($y = 1.1568x - 7.2415$, $r = 0.7143$, $p < 0.001$; Fig. 2A), and IL-6 ($y = 2.4049x + 0.593$, $r = 0.6409$, $p < 0.001$; Fig. 2B) levels; and the increase rate of the IL-10 levels ($y = -1.0622x + 33.434$, $r = -0.3299$, $p < 0.01$; Fig. 2-C). Subjects who had high UAGT levels at baseline exhibited a high ACR reduction rate ($y = -1.0876x - 10.147$, $r = -0.3599$, $p < 0.05$; Fig. 3).

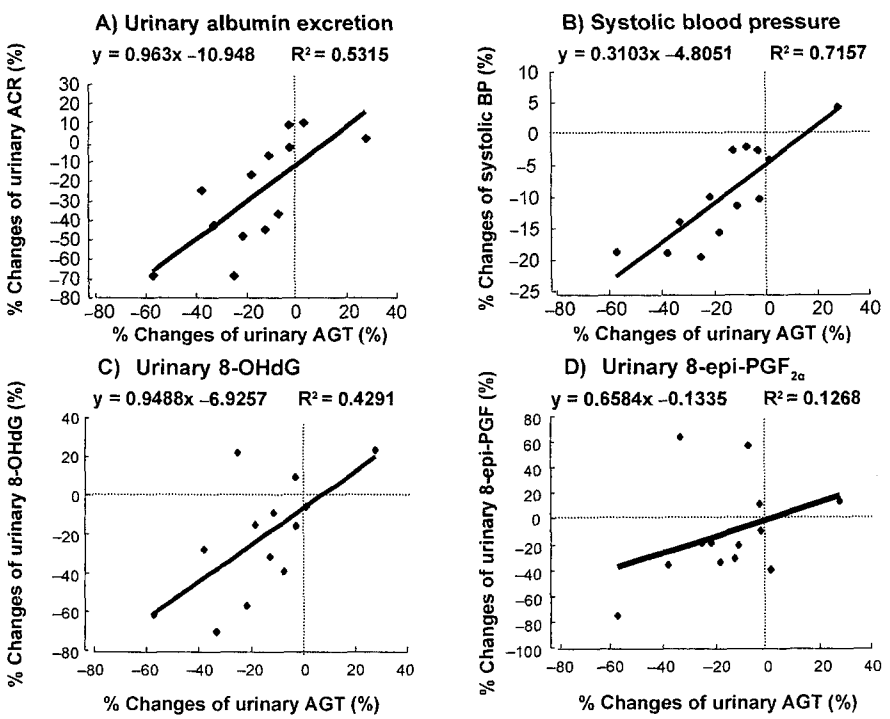

Figure 1. Correlation between the reduction rate of the urinary angiotensinogen (UAGT) levels and that of urinary albumin excretion (ACR): **A)** reduction rate of systolic blood pressure (SBP): **B)** reduction rates of the urinary 8-hydroxydeoxyguanosine (8-OHdG) and urinary 8-epi-prostaglandin F2α (8-epi-PGF2α) levels.