厚生労働科学研究研究費補助金

長寿科学総合研究事業

合併症発症進展を見据えた糖尿病食事療法の開発推進に関する研究

平成１６年度　総括・分担研究報告書

主任研究者　清野　裕

平成１７（２００５）年　４月

目　　次

厚生労働科学研究費補助金（長寿科学総合研究事業）
（総括）研究報告書

合併症発症進展を見据えた糖尿病食事療法の開発推進に関する研究

（主任研究者）清野　裕　関西電力病院長

研究要旨
食生活の急激な変化に対応する、最新の栄養素摂取や糖尿病合併症発症に関する基礎的な研究成果を取りいれた食事療法のエビデンスの確立と一般臨床の場への導入が望まれている。本年度は、現代の食生活に近い組成で構成した食事負荷症例を増加させ、目標180症例の70%を達成した。食事組成の代謝動態への影響の解析とともに、本年度は、膵島量がインスリンの基礎分泌量のみならず追加分泌量の指標となり、その計算式と2型糖尿病症例への応用を明らかにした。さらに日本人2型糖尿病のインスリン抵抗性を規定する因子を探索し、血清中性脂肪、E-selectin、leptinが独立してインスリン抵抗性に寄与していることを明らかにした。

（分担研究者）
山田　祐一郎　　京都大学
谷口　中　　関西電力病院
幣　　憲一郎　　京都大学

A. 研究目的

わが国でも高齢化とともに糖尿病に罹患する患者数は過去40年間において70倍と激増し、740万にも達することが報告されている。さらには、糖尿病に伴って生じる合併症、すなわち、大血管や細小血管の動脈硬化によって発症する心筋梗塞や脳梗塞さらには腎不全や失明によって生じる生命予後やQOLの不良が深刻な社会問題となっており、医療経済的にも社会に大きな負担を強いている。

糖尿病は、食事療法・運動療法・薬物療法が治療の柱であるが、特に食事療法の重要性は高く、医療費の抑制の視点から科学的根拠を持った食事療法の確立が必須である。従来は摂取エネルギー量の制限が中心となっているが、最新の個別の栄養素摂取や糖尿病合併症発症に関する基礎的な研究成果を取りいれた食事療法のエビデンスの確立と一般臨床の場への導入が望まれている。

糖尿病の病態を考えるにあたり、インスリン分泌障害とインスリン抵抗性がその大きな成因であると考えられている。消化管ホルモン分泌の低下はインスリン分泌を低下させ耐糖能を悪化させる一方、消化管ホルモン分泌の増加は肥満・インスリン抵抗性を来たし耐糖能を悪化させる。本研究は食事による消化管ホルモンの変化を明らかにすることによって、より的確な食事療法を行うことを目指している。すなわち、インスリン分泌障害を主体とした糖尿病症例には消化管ホルモン分泌が亢進する食事、インスリン抵抗性を主体とした糖尿病には消化管ホルモン分泌が低下する食事の指導を目指している。

本年度は食事負荷試験の被験者数を増加させるとともに、インスリン抵抗性やインスリン分泌障害の指標を明らかにすることを試みた。

B. 研究方法

全体研究と個別研究に分けて記載する

全体研究

入院・外来の2型糖尿病患者に対して、年齢、罹病期間、家族歴、治療歴などの患者背景、身長、体重、ウエストヒップ比などの身体所見、血糖、HbA1c、インスリン値、脂質などの一般的な血液検査所見、眼科診、尿中微量アルブミン、振動覚、頚動脈中膜内膜肥厚などの糖尿病細小血管ならびに大血管合併症の検索、グルカゴン負荷試験によるインスリン分泌能の評価など、調査・データ収集を行う。

さらに、エネルギー451kcal、蛋白17.2g、脂質16.6g、炭水化物57.6gの基準食を用い、経時的に血糖、インスリン値、Cペプチド値、GIP値、GLP1値ならびに脂質値を測定する。

また、自宅での自宅での食事の記載とその解析によって、摂取エネルギー、蛋白質・脂質・糖質量を推定するとともに、経時的に行うことによって、食事記入得られた食事摂取状況と、食事負荷試験で得られた糖・脂質処理能を対比させて検討する。なお、本研究計画は、関西電力病院ならびに京都大学医学部附属病院において、すでに倫理委員会の承認が得られている。

個別研究

1) 本研究の意義、必要性を理解し同意の得られた43-84歳のBMI２７kg/m2未満の2型糖尿病患者97名（平均糖尿病罹病期間11.2年、平均BMI 23.0kg/m2、平均HbA1c 7.0 %）を対象にBMI、空腹時血糖、血清脂質（中性脂肪、総コレステロール、HDLコレステロール）、血清インスリン、可溶性E-selectin、leptinを測定した。LDLコレステロールはFriedewald formulaにて算出した。インスリン抵抗性はHOMA-IRにて評価し、HOMA-IR>2.5をインスリン抵抗性群、HOMA-IR<2.5をインスリン感受性群と定義し両群の臨床背景につき可溶性E-selecin, leptin、血清TGを中心に検討した。

2) 4症例計6回の膵島移植後の症例について、空腹時の血糖と空腹時の血清Cペプチドを測定し、その相関を検討した。

3) 上記で得られた指標 SUIT (Secretory Units of Islets in Transplantation) について、304名の2型糖尿病症例を算出するとともに、グルカゴン負荷試験で得られた6分後の血清Cペプチド値と比較検討した。

C. 研究成果

全体研究については、目標180症例の2/3を超えており、順調に進捗し、食後高血糖・食後高脂血症など日本人独自の2型糖尿病のエビデンスが集積しつつある。

日本人2型糖尿病の病態は膵島量により強く影響を受けている可能性が指摘されていたため、症例を申請者らが提唱する新たな膵島量を反映するSUIT指数（下記に記載）で分類し、50未満を膵島不足群、50以上を膵島充足群とした。正常耐糖能者では、血糖(mg/dl)は前値の91.1±2.0に対し、1時間値97.7±5.3、2時間値92.5±4.5であり、中性脂肪((mg/dl)は前値86.0±10.7、1時間値94.1±10.4、2時間値105.4±12.5であったが、膵島不足群においては血糖の上昇が顕著で前値149.2±6.2、1時間値229.1±6.8、2時間値230.6±10.6であり、膵島充足群のそれぞれ107.5±4.1、167.9±7.0、168.9±10.8に比しも有意に高値であった。一方、中性脂肪については、膵島充足群で前値110.1±11.5、1時間値119.0±11.6、2時間値134.9±13.6であり、膵島不足群のそれぞれ99.0±9.0、111.1±10.8、118.6±10.4に対し高値の傾向を示した。すなわち、膵島不足群ではインスリン分泌不足によって高血糖を示す一方、膵島充足群はインスリンの作用障害のため、高中性脂肪血症を示し、個々の症例に応じた食事療法の重要性が示された。

個別研究について、インスリン抵抗性と種々の因子の関与度について多変量解析を行ったところ、インスリン抵抗性の説明因子としてE-selectin (F=18.4.)、TG (F=19.3)、leptin (F=14.0)がそれぞれ有意な独立説明変数であり、これら３因子でインスリン抵抗性の４５％を説明し得た。また、膵島移植症例の解析から血清Cペプチド値を空腹時血糖から61.8引いた値で割った値がインスリン分泌能を反映しているものと考えら、正常耐糖能者の解析で正常者が100となるように係数を

設定し、得られた値をSUIT (Secretory Units of Islets in Transplantation)と命名した。2型糖尿病症例において指標 SUIT とグルカゴン負荷6分後の血清Cペプチド値との相関を検討した。その結果、この2つの指標は強い相関を持つことが明らかとなり、SUITは2型糖尿病症例においてもインスリン分泌の良好な指標となると考えられた。

D. 考察

インスリン分泌障害を主体とした糖尿病症例には消化管ホルモン分泌が亢進する食事、インスリン抵抗性を主体とした糖尿病には消化管ホルモン分泌が低下する食事の指導が必要であり、この両者を的確に鑑別する必要がある。

BMI27kg/m2未満の日本人2型糖尿病のインスリン抵抗性を規定する独立した因子に血清中性脂肪以外にE-selectin、leptinが考えられた。E−selectin, レプチンは血清中性脂肪と並び近年心血管病変との関連性が指摘されており、２型糖尿病におけるインスリン抵抗性と慢性血管合併症の関連性を裏付ける上で重要であることが示唆された。現在の食事組成とこれら抵抗性因子の関連について解析に入っている。今後栄養そのものが慢性血管合併症の発症において重要であるか否かを評価する必要がある。

また、インスリン分泌能については従来定量性に乏しかったが、今回得られた指標SUITはHOMA-βと類似しているが、HOMA-βはインスリン治療中の症例には使えないのに対し、SUITは外来性に注射して投与するインスリン量がダイナミックに変動する膵島移植後においても一定値を示していた。また、わが国でよく使われるグルカゴン負荷試験とよく相関することが明らかとなった。SUITは空腹時の1回採血だけで算出できるので、より簡便な指標と考えられる。この指標をもとに、分泌と抵抗性の関連を解析している。

本指標で糖尿病症例を分別することにより、より的確な食事療法に繋がることが期待される。

E. 結論

膵島量がインスリンの基礎分泌量のみならず追加分泌量の指標となり、その計算式と2型糖尿病症例への応用を明らかにするとともに、日本人2型糖尿病のインスリン抵抗性を規定する因子を探索し、血清中性脂肪、E-selectin、leptinが独立してインスリン抵抗性に寄与していることを明らかにした。食事組成のこれらに対する影響を明らかにすることは、根拠を持った食事療法の的確化に繋がるものと期待される。

F. 健康危険情報

なし

G. 研究発表

1. 論文発表

1) Taniguchi A, Fukushima M, Nakai Y, Kuroe A, Yamano G, Yanagawa T, Ohgushi M, Ohya M, Yoshii S, Taki Y, Seino Y.: Soluble E-selectin, leptin, triglycerides, and insulin resistance in nonobese Japanese type 2 diabetic patients. Metabolism 54(3):376-80, 2005.

2) Fukushima M, Usami M, Ikeda M, Nakai Y, Taniguchi A, Matsuura T, Suzuki H, Kurose T, Yamada Y, Seino Y. Insulin secretion and insulin sensitivity at different stages of glucose tolerance: a cross-sectional study of Japanese type 2 diabetes. Metabolism 53(7):831-5, 2004.

3) Suzuki H, Fukushima M, Usami M, Ikeda M, Taniguchi A, Nakai Y, Matsuura T, Yasuda K, Hosokawa M, Seino Y, Yamada Y. IGT with fasting hyperglycemia is more strongly associated with microalbuminuria than IGT without fasting hyperglycemia. Diabetes Res Clin Pract 64(3):213-9, 2004

4) 任和子、津田謹輔、谷口中、福島光夫、北谷直美、奥村裕英、長谷川順子、中井義勝　2型糖尿病患者における糖尿病に関連した日常生活のストレス原因に対するコーピングと血糖コントロールの関連　糖尿病 47(11):883-888、2004.

5) Yamada Y, Seino Y. Physiology of GIP-

-a lesson from GIP receptor knockout mice. Horm Metab Res 36(11-12):771-4, 2004
6) Radu RG, Fujimoto S, Mukai E, Takehiro M, Shimono D, Nabe K, Shimodahira M, Kominato R, Aramaki Y, Nishi Y, Funakoshi S, Yamada Y, Seino Y. Tacrolimus suppresses glucose-induced insulin release from pancreatic islets by reducing glucokinase activity. Am J Physiol 288(2):E365-71, 2005.
7) Takehiro M, Fujimoto S, Shimodahira M, Shimono D, Mukai E, Nabe K, Radu RG, Kominato R, Aramaki Y, Seino Y, Yamada Y. Chronic exposure to beta-hydroxybutyrate inhibits glucose-induced insulin release from pancreatic islets by decreasing NADH contents. Am J Physiol 288(2):E372-80, 2005.
8) Tsukiyama K, Yamada Y, Miyawaki K, Hamasaki A, Nagashima K, Hosokawa M, Fujimoto S, Takahashi A, Toyoda K, Toyokuni S, Oiso Y, Seino Y. Gastric inhibitory polypeptide is the major insulinotropic factor in K(ATP) null mice. Eur J Endocrinol. 151(3):407-12, 2004.
9) 山田祐一郎、松本愼一、福田一仁、濱崎暁洋、小倉雅仁、松岡啓子、藤本新平、興津輝、岩永康裕、野口洋文、米川幸秀、永田英生、柴田登志也、笠井泰成、前川平、清野裕、田中紘一　心停止ドナーからの膵島移植によってインスリン離脱した1型糖尿病の一症例　糖尿病 47(12): 945-950, 2004.

２．学会発表

1) 北谷直美、辻とも子、黒江彰、谷口中、清野裕　食事調査から糖尿病患者の食事の問題点と指導ポイントを考える　日本病態栄養学年次学術集会（平成17年1月）
2) 小倉雅仁、谷口中、黒江彰、福島光夫、中井義勝、長坂昌一郎、山田祐一郎、清野裕　日本人2型糖尿病の炎症マーカー(IL-6・CRP)について　日本糖尿病学会年次学術集会（平成16年5月）
3) 浦瀬真理子、山本奈穂子、中西祐子、幣憲一郎、田中清、山田祐一郎、木戸詔子　糖尿病食事療法におけるQOLの評価　日本病態栄養学年次学術集会（平成17年1月）

H．知的財産権の出願・登録状況

なし

厚生労働科学研究費補助金（長寿科学総合研究事業）
（分担）研究報告書

日本人２型糖尿病のインスリン抵抗性に寄与する因子に関する研究

（主任研究者）清野　裕　関西電力病院長
（分担研究者）谷口　中　関西電力病院

研究要旨
BMI 27未満の日本人2型糖尿病のインスリン抵抗性を規定する因子を探索し、血清中性脂肪、E-selectin、leptinが独立してインスリン抵抗性に寄与していることを明らかにした。

A. 研究目的

インスリン抵抗性は２型糖尿病の発症進展のみならず慢性血管合併症の発症進展に関連性が高いと言われている。一方、接着分子、レプチン、脂質異常も心血管合併症とのからみが指摘されている。そこで申請者らは白人など他の人種に比しインスリン抵抗性の寄与度を容易に評価し得る日本人２型糖尿病患者において接着分子（可溶性E-selectin）に加え血清レプチン、血清中性脂肪を含む脂質異常とインスリン抵抗性の関連性につき検討した。

B. 研究方法

本研究の意義、必要性を理解し同意の得られた43-84歳のBMI２７kg/m2未満の2型糖尿病患者97名（平均糖尿病罹病期間11.2年、平均BMI 23.0kg/m2、平均HbA1c　7.0 %）を対象にBMI、空腹時血糖、血清脂質（中性脂肪、総コレステロール、HDLコレステロール）、血清インスリン、可溶性E-selectin、leptinを測定した。LDLコレステロールはFriedewald formulaにて算出した。インスリン抵抗性はHOMA-IRにて評価し、HOMA-IR>2.5をインスリン抵抗性群（以下R-SI）、HOMA-IR<2.5をインスリン感受性群（以下N-SI）と定義し両群の臨床背景につき可溶性E-selecin, leptin、血清TGを中心に検討した。

C. 研究成果

R-S群はN-SI群に比し、可溶性E-selectin、leptin、中性脂肪、総コレステロール、LDLコレステロール、拡張期血圧が有意に大であった。しかしながら年齢、性別、糖尿病罹病期間、BMI、収縮期血圧、HbA1c、HDLコレステロールには両群で有意な差はみられなかった。単変量解析にて検索したところ、HOMA-IRはE-selectin、leptin、中性脂肪、BMI、収縮期血圧、拡張期血圧、総コレステロール、LDLコレステロール、HbA1cと有意な正相関を認めた。これら多くの因子の関与度をさらに詳細に検討すべく多変量解析を行ったところ、HOMA-IRの説明因子としてE-selectin (F=18.4.)、TG (F=19.3)、leptin (F=14.0)がそれぞれ有意な独立説明変数であり、これら３因子でHOMA-IRの４５％を説明し得た。

D. 考察

BMI27kg/m2未満の日本人2型糖尿病のインスリン抵抗性を規定する独立した因子に血清中性脂肪以外にE-selectin、leptinが考えられた。E－selectin, レプチンは血清中性脂肪と並び近年心血管病変との関連性が指摘されており、２型糖尿病におけるインスリン抵抗性と慢性血管合併症の関連性を裏付ける上で重要であることが示唆された。今後栄養そのものが慢性血管合併症の発症において重要であるか否かを評価する必要がある。この点において今回得られた研究結果はこれら３因

子を新たな慢性血管合併症と栄養の関連性を結びつける上で重要な要素と考え現在食事負荷を行いつつ検討している。

E. 結論

BMI 27未満の日本人2型糖尿病のインスリン抵抗性を規定する因子を探索し、血清中性脂肪、E-selectin、leptinが独立してインスリン抵抗性に寄与していることを明らかにした。

F. 健康危険情報

なし

G. 研究発表

1. 論文発表

1) Taniguchi A, Fukushima M, Nakai Y, Kuroe A, Yamano G, Yanagawa T, Ohgushi M, Ohya M, Yoshii S, Taki Y, Seino Y.: Soluble E-selectin, leptin, triglycerides, and insulin resistance in nonobese Japanese type 2 diabetic patients. Metabolism 54(3):376-80, 2005.

2) Fukushima M, Usami M, Ikeda M, Nakai Y, Taniguchi A, Matsuura T, Suzuki H, Kurose T, Yamada Y, Seino Y. Insulin secretion and insulin sensitivity at different stages of glucose tolerance: a cross-sectional study of Japanese type 2 diabetes. Metabolism 53(7):831-5, 2004.

3) Suzuki H, Fukushima M, Usami M, Ikeda M, Taniguchi A, Nakai Y, Matsuura T, Yasuda K, Hosokawa M, Seino Y, Yamada Y. IGT with fasting hyperglycemia is more strongly associated with microalbuminuria than IGT without fasting hyperglycemia. Diabetes Res Clin Pract 64(3):213-9, 2004

4) 任和子、津田謹輔、谷口中、福島光夫、北谷直美、奥村裕英、長谷川順子、中井義勝　2型糖尿病患者における糖尿病に関連した日常生活のストレス原因に対するコーピングと血糖コントロールの関連　糖尿病 47(11):883-888、2004

2. 学会発表

1) 北谷直美、辻とも子、黒江彰、谷口中、清野裕　食事調査から糖尿病患者の食事の問題点と指導ポイントを考える　日本病態栄養学年次学術集会（平成17年1月）

2) 小倉雅仁、谷口中、黒江彰、福島光夫、中井義勝、長坂昌一郎、山田祐一郎、清野裕　日本人2型糖尿病の炎症マーカー(IL-6・CRP)について　日本糖尿病学会年次学術集会（平成16年5月）

H. 知的財産権の出願・登録状況

なし

厚生労働科学研究費補助金（長寿科学総合研究事業）
（分担）研究報告書

日本人２型糖尿病のインスリン抵抗性に寄与する因子に関する研究

（分担研究者）山田　祐一郎　京都大学
（分担研究者）幣　　憲一郎　京都大学

研究要旨
食事療法の指示にあたり、個々の糖尿病症例のインスリン分泌量は重要である。平成16年度から本邦でも開始された膵島移植の症例の解析から、膵島量を空腹時血糖と空腹時血清Cペプチドの二つから推定する計算式を導き出した。本計算式から得られる指標（SUIT: Secretory Units of Islets in Transplantation）を2型糖尿病症例に当てはめると、グルカゴン負荷6分後の血清Cペプチド値と強く相関することが明らかとなった。したがって、SUITはインスリンの基礎分泌のみならず追加分泌の指標となり、食事指導に当たり、非常に有益であると考えられた。

A. 研究目的

糖尿病の病態を考えるにあたり、インスリン分泌障害とインスリン抵抗性がその大きな成因であると考えられている。消化管ホルモン分泌の低下はインスリン分泌を低下させ耐糖能を悪化させる一方、消化管ホルモン分泌の増加は肥満・インスリン抵抗性を来たし耐糖能を悪化させる。したがって、食事による消化管ホルモン分泌増加はインスリン分泌障害を有する症例では必要だが、インスリン抵抗性の症例ではかえって病態を悪化させる。したがって、インスリン分泌能を明らかにすることは、より的確な食事療法を行うにあたり非常に重要であると考えられる。しかしながら、簡単にインスリン分泌能を評価する指標はない。

膵島移植はアルバータ大学のグループが2000年に新たな免疫抑制薬などを用いた方法を発表して以来、欧米で急速に普及してきた。欧米では脳死ドナーからの膵島単離であるが、本邦においては、法律によって脳死からの単離は認められておらず、心臓死ドナーから提供された膵島を移植に用いる必要があり、より単離法が困難なため実施が遅れていたが、2004年4月に京都大学で開始された。本治療のいては、膵島をほとんど有していないレシピエントに正常な機能を有するドナーの膵島を移植するため、移植後に得られるレシピエントのインスリン分泌能は基本的に膵島の数によって規定されているものと考えられる。

そこで、膵島移植症例のインスリン分泌能を評価する指標の作製を試みた。

B. 研究方法

1) 4症例計6回の膵島移植後の症例について、空腹時の血糖と空腹時の血清Cペプチドを測定し、その相関を検討した。
2) 上記で得られた指標 SUIT (Secretory Units of Islets in Transplantation) について、304名の2型糖尿病症例を算出するとともに、グルカゴン負荷試験で得られた6分後の血清Cペプチド値と比較検討した。

C. 研究成果

1) 各症例について測定した空腹時の血糖をX

軸、空腹時の血清Cペプチドを Y軸にとってプロットした。その結果、いずれの場合もX軸との切片は血糖60mg/dl強であり、直線上に位置することが明らかとなった。全症例で統計処理を行うとその切片は61.8mg/dlである。したがって、血清Cペプチド値を空腹時血糖から61.8引いた値で割った値がインスリン分泌能を反映しているものと考えられた。正常耐糖能者の解析で正常者が100となるように係数を設定し、得られた値をSUIT (Secretory Units of Islets in Transplantation) と命名した。

2) 2型糖尿病症例において指標 SUIT とグルカゴン負荷6分後の血清Cペプチド値との相関を検討した。その結果、この2つの指標は強い相関を持つことが明らかとなり、SUITは2型糖尿病症例においてもインスリン分泌の良好な指標となると考えられた。

D. 考察

指標SUITと現在まで知られている指標について考察する。

まず、HOMA-βは空腹時の血糖とインスリン値から導き出される指標でSUITと類似した計算式を持つ。最も大きな違いは、HOMA-βはインスリン治療中の症例には使えないことである。それに対してSUITはインスリン量がダイナミックに変動する膵島移植後においても一定値を示していた。

また、わが国でよく使われるグルカゴン負荷試験とよく相関することが明らかとなった。SUITは空腹時の1回採血だけで算出できるので、より簡便な指標と考えられる。

本指標で糖尿病症例を分別することにより、より的確な食事療法に繋がることが期待される。

E. 結論

膵島移植の症例の解析から、膵島量を空腹時血糖と空腹時血清Cペプチドの二つから推定する指標 (SUIT: Secretory Units of Islets in Transplantation) を導き、2型糖尿病症例においても、グルカゴン負荷6分後の血清Cペプチド値と強く相関することが明らかにした。したがって、SUITはインスリンの基礎分泌のみならず追加分泌の指標となり、食事指導に当たり、非常に有益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

1) Yamada Y, Seino Y. Physiology of GIP--a lesson from GIP receptor knockout mice. Horm Metab Res 36(11-12):771-4, 2004

2) Radu RG, Fujimoto S, Mukai E, Takehiro M, Shimono D, Nabe K, Shimodahira M, Kominato R, Aramaki Y, Nishi Y, Funakoshi S, Yamada Y, Seino Y. Tacrolimus suppresses glucose-induced insulin release from pancreatic islets by reducing glucokinase activity. Am J Physiol 288(2):E365-71, 2005.

3) Takehiro M, Fujimoto S, Shimodahira M, Shimono D, Mukai E, Nabe K, Radu RG, Kominato R, Aramaki Y, Seino Y, Yamada Y. Chronic exposure to beta-hydroxybutyrate inhibits glucose-induced insulin release from pancreatic islets by decreasing NADH contents. Am J Physiol 288(2):E372-80, 2005.

4) Tsukiyama K, Yamada Y, Miyawaki K, Hamasaki A, Nagashima K, Hosokawa M, Fujimoto S, Takahashi A, Toyoda K, Toyokuni S, Oiso Y, Seino Y. Gastric inhibitory polypeptide is the major insulinotropic factor in K(ATP) null mice. Eur J Endocrinol. 151(3):407-12, 2004.

5) 山田祐一郎、松本愼一、福田一仁、濱崎暁洋、小倉雅仁、松岡啓子、藤本新平、興津輝、岩永康裕、野口洋文、米川幸秀、永田英生、柴田登志也、笠井泰成、前川平、清野裕、田中紘一　心停止ドナーからの膵島移植によってインスリン離脱した1型糖尿病の一症例　糖尿病 47(12): 945-950,

2004.　　病態栄養学年次学術集会（平成17年1月）

２．学会発表

1) 浦瀬真理子、山本奈穂子、中西祐子、幣憲一郎、田中清、山田祐一郎、木戸詔子　糖尿病食事療法におけるQOLの評価　日本

H．知的財産権の出願・登録状況

なし

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
Taniguchi A, Fukushima M, Nakai Y, Kuroe A, Yamano G, Yanagawa T, Ohgushi M, Ohya M, Yoshii S, Taki Y, Seino Y.	Soluble E-selectin, leptin, triglycerides, and insulin resistance in nonobese Japanese type 2 diabetic patients.	Metabolism	54(3)	376-80	2005
Fukushima M, Usami M, Ikeda M, Nakai Y, Taniguchi A, Matsuura T, Suzuki H, Kurose T, Yamada Y, Seino Y.	Insulin secretion and insulin sensitivity at different stages of glucose tolerance: a cross-sectional study of Japanese type 2 diabetes.	Metabolism	53(7)	831-5	2004
Suzuki H, Fukushima M, Usami M, Ikeda M, Taniguchi A, Nakai Y, Matsuura T, Yasuda K, Hosokawa M, Seino Y, Yamada Y.	IGT with fasting hyperglycemia is more strongly associated with microalbuminuria than IGT without fasting hyperglycemia.	Diabetes Res Clin Pract	64(3)	213-9	2004
任和子、津田謹輔、谷口中、福島光夫、北谷直美、奥村裕英、長谷川順子、中井義勝	2型糖尿病患者における糖尿病に関連した日常生活のストレス原因に対するコーピングと血糖コントロールの関連	糖尿病	47(11)	883-888	2004
Yamada Y, Seino Y.	Physiology of GIP--a lesson from GIP receptor knockout mice.	Horm Metab Res	36(11-12)	771-4	2004
Radu RG, Fujimoto S, Mukai E, Takehiro M, Shimono D, Nabe K, Shimodahira M, Kominato R, Aramaki Y, Nishi Y, Funakoshi S, Yamada Y, Seino Y.	Tacrolimus suppresses glucose-induced insulin release from pancreatic islets by reducing glucokinase activity.	Am J Physiol	288(2)	E365-71	2005

Takehiro M, Fujimoto S, Shimodahira M, Shimono D, Mukai E, Nabe K, Radu RG, Kominato R, Aramaki Y, Seino Y, Yamada Y.	Chronic exposure to beta-hydroxybutyrate inhibits glucose-induced insulin release from pancreatic islets by decreasing NADH contents.	Am J Physiol	288(2)	E372-80	2005
Tsukiyama K, Yamada Y, Miyawaki K, Hamasaki A, Nagashima K, Hosokawa M, Fujimoto S, Takahashi A, Toyoda K, Toyokuni S, Oiso Y, Seino Y.	Gastric inhibitory polypeptide is the major insulinotropic factor in K(ATP) null mice.	Eur J Endocrinol	151(3)	407-12	2004
山田祐一郎、松本愼一、福田一仁、濱崎暁洋、小倉雅仁、松岡啓子、藤本新平、興津輝、岩永康裕、野口洋文、米川幸秀、永田英生、柴田登志也、笠井泰成、前川平、清野裕、田中紘一	心停止ドナーからの膵島移植によってインスリン離脱した1型糖尿病の一症例	糖尿病	47(12)	945-950	2004

Available online at www.sciencedirect.com

SCIENCE DIRECT

Metabolism Clinical and Experimental 54 (2005) 376–380

Metabolism
Clinical and Experimental

www.elsevier.com/locate/metabol

Soluble E-selectin, leptin, triglycerides, and insulin resistance in nonobese Japanese type 2 diabetic patients

Ataru Taniguchi[a,*], Mitsuo Fukushima[b], Yoshikatsu Nakai[c], Akira Kuroe[a], Gen Yamano[a], Takiko Yanagawa[a], Minako Ohgushi[a], Michihiro Ohya[a], Satoru Yoshii[a], Yoshiro Taki[a], Yutaka Seino[a]

[a]*Division of Diabetes and Clinical Nutrition, Kansai-Denryoku Hospital, Osaka 553-0003, Japan*
[b]*Department of Health Informatics Research, Translational Research Informatics Center, Kobe 650-0047, Japan*
[c]*School of Health Sciences, Faculty of Medicine, Kyoto University, Kyoto 606-8507, Japan*

Received 13 July 2004; accepted 18 October 2004

Abstract

The aim of the present study was to investigate the relationships between insulin resistance and soluble E-selectin, body mass index (BMI), leptin, and serum lipid profile including triglycerides in nonobese Japanese type 2 diabetic patients.

A total of 97 nonobese Japanese type 2 diabetic patients aged 43 to 84 years were examined. The duration of diabetes was 11.2 ± 0.8 years. In conjunction with BMI and fasting concentrations of plasma glucose, serum lipids (triglycerides, total cholesterol, and high-density lipoprotein cholesterol) and serum insulin, soluble E-selectin, and leptin were also measured. The low-density lipoprotein (LDL) cholesterol level was calculated using the Friedewald formula. Insulin resistance was estimated by the homeostasis model assessment. The subjects were divided into 2 groups according to the value of insulin resistance estimated by the homeostasis model assessment. Values greater than 2.5 were indicative of the insulin-resistant state, and values less than 2.5 were indicative of the insulin-sensitive state.

The insulin-resistant group had significantly higher levels of E-selectin, leptin, triglycerides, total and LDL cholesterol, and diastolic blood pressure as compared with the insulin-sensitive group. There was, however, no significant difference in age, sex, diabetes duration, BMI, systolic blood pressure, HbA1c, and high-density lipoprotein cholesterol between the 2 groups. Univariate regression analysis showed that insulin resistance was positively correlated to E-selectin ($r = 0.305$, $P = .003$), BMI ($r = 0.283$, $P = .006$), leptin ($r = 0.296$, $P = .004$), HbA1c ($r = 0.241$, $P = .018$), serum triglycerides ($r = 0.385$, $P < .001$), serum total ($r = 0.240$, $P = .019$) and LDL cholesterol ($r = 0.254$, $P = .013$) levels, and systolic ($r = 0.247$, $P = .024$) and diastolic ($r = 0.305$, $P = .006$) blood pressure. Multiple regression analyses showed that insulin resistance was independently predicted by serum E-selectin ($F = 18.4$), serum leptin ($F = 14.0$) and serum triglycerides ($F = 20.0$) levels, which explained 45.0% of the variability of insulin resistance.

From these results, it can be concluded that in conjunction with serum triglycerides and serum leptin, serum E-selectin is another important independent factor associated with insulin resistance in nonobese Japanese type 2 diabetic patients.

1. Introduction

Type 2 diabetes is a heterogeneous syndrome characterized by insulin resistance and/or defective insulin secretion [1,2]. There seem to be ethnic differences in insulin resistance in type 2 diabetes. Nonobese Japanese type 2 diabetic patients are unique in that they are divided into 2 variants: one with insulin resistance and the other with normal insulin sensitivity [3,4].

The mechanisms underlying insulin resistance in nonobese Japanese type 2 diabetes are not fully understood. We recently demonstrated that insulin resistance in nonobese Japanese type 2 diabetic patients is mostly associated with triglycerides but not with body mass index (BMI) [5,6]. The reduction in triglycerides level by bezafibrate [7] or exercise [8] leads to an enhancement in insulin action without affecting BMI in nonobese Japanese type 2 diabetic patients. Abassi et al [9] are the first to show that plasma insulin concentration is more tightly linked to plasma leptin concentration than is the BMI in human beings. Thus, in conjunction with serum triglycerides, leptin is suggested to

* Corresponding author. Fax: +81 6 6458 6994.
E-mail address: K-58403@kepco.co.jp (A. Taniguchi).

0026-0495/$ – see front matter © 2005 Elsevier Inc. All rights reserved.
doi:10.1016/j.metabol.2004.10.006

be another factor that is linked to insulin resistance in nonobese Japanese type 2 diabetic patients.

Furthermore, there are some literatures suggesting that insulin resistance is closely associated with the pathogenesis of atherosclerosis. The earliest morphological evidence of atherosclerosis is the attachment of monocytes to the cell surface of the endothelium. Monocytes attach at the cell surface of adhesion molecules such as E-selectin, intercellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1). In contrast to ICAM-1 and VCAM-1, E-selectin is expressed only on activated endothelium [10]. Thus, E-selectin is hypothesized to be one of the most important adhesion molecules for the evolution of atherosclerosis. Whereas serum E-selectin level is reported to be high in type 2 diabetic patients, the relationship between serum concentration of E-selectin and insulin resistance is very limited [11-13]. Furthermore, the relationship has not yet been fully investigated in nonobese Japanese type 2 diabetic patients without confounding the effects of serum triglycerides and serum leptin levels. In this respect, a major problem is that the degree of overweight or of hyperglycemia, insulin therapy, or the medications known to improve insulin resistance is shown to affect serum soluble E-selectin level. Thus, the aim of the present study is to investigate the relationship between insulin resistance andÂserum E-selectin in nonobese unique Japanese type 2 diabetic patients taking into account of the effects of leptin, triglycerides, BMI, and hemoglobin (Hb) A1c. This is the first description that in conjunction with serum triglycerides and serum leptin, serum E-selectin is another independent factor closely associated with insulin resistance in nonobese Japanese type 2 diabetic patients who had no insulin therapy and no evidence of diabetic vascular complications.

2. Subjects and methods

Ninety-seven Japanese type 2 diabetic patients who visited our clinic were enrolled for the present study. Type 2 diabetes mellitus was diagnosed based on the criteria of the World Health Organization [14]. The patients who had chronic heart or renal failure, symptomatic coronary heart disease, symptomatic stroke, and symptomatic peripheral artery disease were excluded. They had no evidence of current acute illness including clinically significant infectious disease. Their age and BMI levels were 62.9 ± 0.9 years (mean ± SEM) and 23.0 ± 0.2 (range, 19.1 to 26.7 kg/m^2), respectively. They all were nonobese [15]. The duration of diabetes was 11.2 ± 0.8 (range, 1 to 35 years). HbA1c level was 7.0% ± 0.1% (range, 5.2% to 10.4%). Systolic and diastolic blood pressure was 137 ± 2 and 83 ± 1 mm Hg, respectively. Forty-two of 97 patients had hypertension that was treated with angiotensin-converting enzyme inhibitors (21/42), calcium-channel blockers (20/42), or both (1/42). Eighty-three patients were taking sulfonylureas (gliclazide) and the rest with diet alone. Seventeen and 14 of 97 patients were treated with bezafibrate and 3-hydroxy-3 methylglutaryl coenzyme A (HMG CoA) reductase inhibitors, respectively. They all were not treated with insulin, biguanides, or pioglitazone. All subjects had ingested at least 150 g of carbohydrate for the 3 days preceding the study. They did not consume alcohol or perform heavy exercise for at least 1 week before the study.

Blood was drawn at the morning after a 12-hour fast. Plasma glucose was measured with glucose oxidase method. The triglycerides, total cholesterol, and high-density lipoprotein (HDL) cholesterol were also measured. Serum insulin was measured using a 2-site immunoradiometric assay (Insulin Riabead II, Dainabot, Japan). Coefficients of variation were 4% for insulin greater than 25 μU/mL and 7% for insulin less than 25 μU/mL, respectively. There was no detectable cross-reactivity of proinsulin in the insulin assay. Soluble E-selectin was measured by commercially available enzyme-linked immunosorbent assay kits (R&D Systems, Minneapolis, Minn) using baseline samples. Serum leptin concentration was measured with a radioimmunoassay kit (Linco Research, St Charles, Mo) using specific human leptin antibody. The intra-assay and interassay CVs were less than 6% for E-selectin and leptin. Samples for insulin, E-selectin, and leptin were prepared, frozen, and stored at −70°C until the assay. The estimate of insulin resistance by homeostasis model assessment (HOMA-IR) was calculated with the formula: fasting serum insulin (μU/mL) × fasting plasma glucose (mmol/L)/22.5 [16]. The HOMA-IR value of normal glucose tolerant subjects was 1.6 ± 0.9 (mean ± SD), and we defined the value greater than 2.5 (mean ± SD of normal glucose-tolerant subjects) as an insulin-resistant state and the value less than 2.5 as an insulin-sensitive state [5,6]. The threshold value for insulin resistance in our study (ie, 2.5) is similar to that (2.77) reported in nonobese subjects with no metabolic disorders reported by Borona et al [17].

3. Statistical analysis

Data are presented as mean ± SEM. Statistical analyses were conducted using the StatView 5 system (StatView, Berkeley, Calif). Means of 2 groups were compared with Student t test. Simple (Spearman rank) correlation coefficients between HOMA-IR and measures of variables were calculated, and a stepwise multiple regression analysis was then used to evaluate the independent association of these variables with HOMA-IR. P value less than .05 was considered as significant. In multivariate analysis, F value ≥4 was considered significant.

4. Results

Table 1 illustrates the mean ± SEM of the clinical characteristics and clinical profile in insulin-resistant and insulin-sensitive nonobese Japanese type 2 diabetic patients. HOMA-IR values in the patients with insulin resistance and normal insulin sensitivity were 3.68 ± 0.25 and 1.63 ±

0.06, respectively. Thirty-two (30%) of 97 type 2 diabetic patients had HOMA-IR of greater than 2.5, indicating that they are insulin-resistant. There was no significant difference in age, duration of diabetes, BMI, HbA1c, and HDL cholesterol levels between the 2 subpopulations. Fasting glucose and insulin concentrations were significantly higher in insulin-resistant group than in insulin-sensitive group. In contrast, the patients with insulin resistance had significantly higher concentrations of E-selectin (58.2 ± 4.2 vs 47.2 ± 2.3 mg/dL, $P = .008$), leptin (6.18 ± 0.73 vs 4.47 ± 0.34 mg/dL, $P = .009$), triglycerides (148 ± 12 vs 109 ± 5 mg/dL, $P < .001$), total (213 ± 6 vs 196 ± 4 mg/dL, $P = .018$), and low-density lipoprotein (LDL) cholesterol (134 ± 6 vs 120 ± 4 mg/dL, $P = .018$) as compared with those with normal insulin sensitivity. Whereas no significant difference was observed in systolic blood pressure, diastolic blood pressure was significantly higher in insulin-resistant group than in insulin-sensitive group. There was no significant difference in the mode of therapy for hypertension or lipidemia between the 2 groups (data not shown).

Spearman rank correlations of insulin resistance with measures of variables were calculated for all our diabetic patients (Table 2). Insulin resistance was positively correlated with E-selectin, leptin, triglycerides, BMI, HbA1c, and total and LDL cholesterol levels. Other variables including age, sex, duration of diabetes, and HDL cholesterol were not associated with insulin resistance.

Multiple regression analyses were carried out using the stepwise procedure. The analysis included insulin resistance as a dependent variable and candidate risk factors (E-selectin, leptin, triglycerides, BMI, HbA1c, total cholesterol, and LDL cholesterol) as independent variables. Insulin resistance was independently predicted by serum concentrations of E-selectin, leptin, and triglycerides, which explained 45.0% of the variability of insulin resistance in our patients. Other variables including BMI, HbA1c, and total and LDL cholesterol were not independently associated with insulin resistance in our nonobese Japanese type 2 diabetic patients.

Table 1
Clinical characteristics and clinical profile in insulin-resistant and insulin-sensitive diabetic patients

	Insulin-resistant	Insulin-sensitive	P
HOMA-IR	3.68 ± 0.25	1.63 ± 0.06	<.001
Number of subjects	32	65	
M/F	30/9	42/5	.384
Age (y)	62.4 ± 1.7	63.1 ± 1.0	.360
BMI (kg/m^2)	23.4 ± 0.3	22.8 ± 0.2	.064
Duration of diabetes (y)	11.3 ± 1.6	11.1 ± 0.8	.459
HbA1c (%)	7.2 ± 0.2	6.9 ± 0.1	.071
HDL cholesterol (mg/dL)	56 ± 2	60 ± 2	.135
Fasting glucose (mg/dL)	151 ± 4	137 ± 3	.005
Fasting insulin (μU/mL)	10.0 ± 0.7	4.8 ± 0.2	<.001
E-selectin (mg/dL)	58.2 ± 4.2	47.2 ± 2.3	.008
Leptin (mg/dL)	6.18 ± 0.73	4.47 ± 0.34	.009
Triglycerides (mg/dL)	148 ± 12	109 ± 5	<.001
Total cholesterol (mg/dL)	213 ± 6	196 ± 4	.018
LDL cholesterol (mg/dL)	134 ± 6	120 ± 4	.018
Systolic blood pressure (mm Hg)	141 ± 3	135 ± 2	.081
Diastolic blood pressure (mm Hg)	88±2	81±1	.001

Table 2
Correlation of insulin resistance to measures of variables in diabetic patients

	r	P
E-selectin	0.305	.003
Leptin	0.296	.004
Triglycerides	0.385	<.001
BMI	0.283	.006
HbA1c	0.241	.018
Total cholesterol	0.240	.019
LDL cholesterol	0.254	.013
Systolic blood pressure	0.247	.024
Diastolic blood pressure	0.305	.006
Age	−0.065	.522
Sex	0.007	.946
HDL cholesterol	−0.178	.804
Duration of diabetes	−0.018	.860

Finally, the relationships between soluble E-selectin and serum leptin, BMI, or serum triglycerides level were investigated. There were no significant relationships between serum soluble E-selectin level and serum leptin, BMI, or serum triglycerides level in our patients (data not shown).

5. Discussion

Type 2 diabetes is a heterogenous syndrome characterized by insulin resistance and/or defective insulin secretion [1,2]. There seems to be ethnic difference in insulin resistance in type 2 diabetes. Haffner et al [18] recently disclosed that 92% of type 2 diabetic patients are insulin-resistant in white populations. In contrast, Chaiken et al [19] previously showed that 60% of type 2 diabetic patients are insulin-resistant in black Americans with a BMI less than 30 kg/m^2. Using minimal model approach shown by Bergman et al [20], our team previously demonstrated that Japanese type 2 diabetic patients are divided into 2 variants: one with primary insulin resistance and the other with normal insulin sensitivity [3,4]. Thereafter, we have shown that 40% of type 2 diabetic patients are insulin-resistant in Japanese populations [5]. In conjunction with the present study that 30% of type 2 diabetic patients are insulin-resistant in nonobese Japanese type 2 diabetic patients, Japanese type 2 diabetic patients are assumed to be unique in terms of clinical profiles.

There are some factors associated with insulin resistance in nonobese Japanese type 2 diabetic patients. We recently demonstrated that serum triglycerides but not BMI are mostly associated with insulin resistance in nonobese Japanese type 2 diabetic patients [5,6]. Thereafter, our group clarified that not only serum leptin but also adiponectin levels are linked to insulin resistance in nonobese Japanese type 2 diabetic patients [21,22]. Serum triglyceride level is positively correlated to visceral fat areas in nonobese Japanese type 2 diabetic patients [23]. Serum

leptin level is positively correlated to subcutaneous fat areas, whereas serum adiponectin level is negatively correlated to visceral fat areas in nonobese Japanese type 2 diabetic patients [21,22]. Thus, the factors associated with insulin resistance in nonobese Japanese type 2 diabetic patients are hypothesized to be linked to adipose tissue–related insulin resistance.

Another factor that is associated with insulin resistance is adhesion molecules such as E-selectin, ICAM-1, and VCAM-1. These adhesion molecules are associated with the evolution of atherosclerosis. Atherosclerosis is assumed to be linked to insulin resistance in human beings. Thus, these adhesion molecules are suggested to be associated with insulin resistance in nonobese Japanese type 2 diabetic patients. In contrast to ICAM-1 and VCAM-1, E-selectin is expressed only on activated endothelium [10]. We therefore investigated the relationship between insulin resistance and serum soluble E-selectin in our nonobese unique Japanese type 2 diabetic patients.

In the present study, we disclosed that not only serum triglyceride but also serum soluble E-selectin and serum leptin levels are higher in insulin-resistant group than in insulin-sensitive groups in nonobese Japanese type 2 diabetic patients matched for sex. Furthermore, in conjunction with serum triglyceride and leptin, E-selectin is independently associated with insulin resistance in nonobese Japanese type 2 diabetic patients. It may be argued that our results are influenced by sex because leptin concentration is influenced by sex. However, not only insulin resistance but also serum triglycerides and E-selectin were not affected by sex in our present study.

Interestingly, serum leptin and triglycerides levels were independently associated with insulin resistance, whereas BMI was not, in our nonobese Japanese type 2 diabetic patients. Serum leptin level is shown to be associated with subcutaneous fat area in nonobese Japanese type 2 diabetic patients [21]. In contrast, serum triglyceride level is shown to be reflective of visceral abdominal fat area in nonobese Japanese type 2 diabetic patients [23]. Thus, body fat distribution but not the degree of BMI seems to affect insulin resistance in nonobese unique Japanese type 2 diabetic patients. This idea is supported from the recent study shown by Abassi et al [9] that plasma insulin concentration is more tightly linked to plasma leptin concentration than is the BMI. We recently demonstrated that both subcutaneous and visceral abdominal fat areas are independently associated with insulin resistance in nonobese Japanese type 2 diabetic patients [23].

E-selectin level was not associated with adipose tissue–related insulin resistance such as leptin, triglycerides, and BMI in our present study. Thus, E-selectin is considered to be another most important factor associated with insulin resistance in nonobese Japanese type 2 diabetic patients.

The mechanisms underlying the relationship between insulin resistance and soluble E-selectin are not known at present. One possible explanation for the relationship is nitric oxide released from endothelium. Steinberg et al [24] showed that insulin resistance is associated with blunted endothelium-dependent vasodilation and that this phenomenon is related to low nitric oxide release from endothelium. Elevated E-selectin level is known to be reflective of endothelial damage [25]. Another possible explanation for the finding is the mode of therapy. Intensive insulin therapy is reported to reduce serum E-selectin level in diabetic patients [26]. Agents that improve insulin resistance are shown to reduce serum E-selectin concentration. Cominacini et al [27] reported that troglitazone decreased serum E-selectin level in patients with type 2 diabetes. In the present study, our patients were not treated with insulin therapy or the medications known to improve insulin resistance such as biguanide or pioglitazone. Finally, the role of oxidative stress should not be overlooked in type 2 diabetic patients. Cominacini et al [11] showed that serum E-selectin concentration is related to plasma hydroperoxides and to susceptibility to LDL to oxidation in type 2 diabetic patients.

Irrespective of this, it can be concluded that in conjunction with serum triglycerides, serum E-selectin and leptin are another independent factors associated with insulin resistance in nonobese unique Japanese type 2 diabetic patients.

References

[1] DeFronzo RA. Lilly Lecture 1987: the triumvirate: beta-cell, muscle, liver: a collusion responsible for NIDDM. Diabetes 1988;37:667-87.
[2] Gerich JE. The genetic basis of type 2 diabetes mellitus: impaired insulin secretion versus impaired insulin sensitivity. Endocr Rev 1988;19:491-503.
[3] Taniguchi A, Nakai Y, Fukushima M, et al. Pathogenic factors responsible for glucose tolerance in patients with NIDDM. Diabetes 1992;41:1540-6.
[4] Nagasaka S, Tokuyama K, Kusaka I, et al. Endogenous glucose production and glucose effectiveness in type 2 diabetic subjects derived from stable-labelled minimal model approach. Diabetes 1999;48:1054-60.
[5] Taniguchi A, Fukushima M, Sakai M, et al. The role of the body mass index and triglyceride levels in identifying insulin-sensitive and insulin-resistant variants in Japanese non–insulin-dependent diabetic patients. Metabolism 2000;49:1001-5.
[6] Taniguchi A, Fukushima M, Sakai M, et al. Remnant-like particle cholesterol, triglycerides, and insulin resistance in nonobese Japanese type 2 diabetic patients. Diabetes Care 2000;23:1766-9.
[7] Taniguchi A, Fukushima M, Sakai M, et al. Effects of bezafibrate on insulin sensitivity and insulin secretion in non-obese Japanese type 2 diabetic patients. Metabolism 2001;50:477-80.
[8] Kishimoto H, Taniguchi A, Fukushima M, et al. Effect of short-term low-intensity exercise on insulin sensitivity, insulin secretion, and glucose and lipid metabolism in non-obese Japanese type 2 diabetic patients. Horm Metab Res 2002;34:27-31.
[9] Abassi F, Carantoni M, McLaughlin T, Reaven GM. Plasma insulin concentration is more tightly linked to plasma leptin concentration than is the body mass index. Metabolism 2000;49:544-7.
[10] Erbe DV, Barry A, Presta LG, et al. Identification of an E-selectin region critical from carbohydrate recognition and cell adhesion. J Cell Biol 1992;119:215-27.
[11] Cominacini L, Pasini F, Garbin U, et al. E-selectin plasma concentration is influenced by glycaemic control in NIDDM patients: possible role of oxidative stress. Diabetologia 1997;40:584-9.

[12] Albertini JP, Valensi P, Lormeau B, et al. Elevated concentrations of soluble E-selectin and vascular cell adhesion molecule-1 in NIDDM. Diabetes Care 1998;21:1008-13.
[13] Matsumoto K, Sera Y, Nakamura H, et al. Serum concentrations of soluble adhesion molecules are related to degree of hyperglycemia and insulin resistance in patients with type 2 diabetes. Diabetes Res Clin Pract 2002;55:131-8.
[14] World Health Organization. Diabetes mellitus: report of a WHO study group. WHO Tech. Rep. Ser. no. 727, 1998.
[15] Taniguchi A, Nakai Y, Doi K, et al. Insulin sensitivity, insulin secretion, and glucose effectiveness in obese subjects: a minimal model analysis. Metabolism 1995;44:1397-400.
[16] Matthews DR, Hosker JP, Rudenski AS, et al. Homeostasis model assessment: insulin resistance and B-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28: 412-9.
[17] Borona E, Kiechl S, Willeit J, et al. Prevalence of insulin resistance in metabolic disorders. The Bruneck Study. Diabetes 1998;47:1643-9.
[18] Haffner SM, D'Agostino Jr R, Mykkanen L, et al. Insulin sensitivity in subjects with type 2 diabetes: relationship to cardiovascular risk factors: the Insulin Resistance Atherosclerosis Study. Diabetes Care 1999;22:562-8.
[19] Chaiken RL, Banerji MA, Pasmantier RM, et al. Patterns of glucose and lipid abnormalities in black NIDDM subjects. Diabetes Care 1991;14:1036-42.
[20] Bergman RN, Phillips LS, Cobelli C. Physiologic evaluation of factors controlling glucose tolerance in man: measurement of insulin sensitivity and B-cell glucose sensitivity from the response to intravenous glucose. J Clin Invest 1981;68:1456-67.
[21] Okumura T, Taniguchi A, Nagasaka S, et al. Relationship of regional adiposity to serum leptin level in nonobese Japanese type 2 diabetic male patients. Diabetes Metab 2003;29:15-8.
[22] Yatagai T, Nagasaka S, Taniguchi A, et al. Hypoadiponectinemia is associated with visceral fat accumulation and insulin resistance in Japanese men with type 2 diabetes mellitus. Metabolism 2003;52: 1274-8.
[23] Taniguchi A, Nakai Y, Sakai M, et al. Relationship of regional adiposity to insulin resistance and serum triglyceride levels in nonobese Japanese type 2 diabetic patients. Metabolism 2002;51: 544-8.
[24] Steinberg HO, Chaker H, Leaming R, et al. Obesity/insulin resistance is associated with endothelial dysfunction. J Clin Invest 1996;97: 2601-10.
[25] Caterina RD, Peng LHB, Thannickal VJ, et al. Nitric oxide decreases cytokine induced endothelial activation. Nitric oxide selectively reduces endothelial expression of adhesion molecules and proinflammatory cytokines. J Clin Invest 1995;96:60-8.
[26] Albertini JP, Valensi P, Lormeau B, et al. Elevated concentrations of soluble. E-selectin and vascular cell adhesion molecule-1 in NIDDM. Effect of intensive insulin treatment. Diabetes Care 1998; 21:1008-13.
[27] Cominacini L, Garbin U, Pasini AF, et al. Troglitazone reduces LDL oxidation and lowers plasma E-selectin concentration in NIDDM. Diabetes 1998;47:130-3.

Metabolism
Clinical and Experimental

VOL 53, NO 7 JULY 2004

Insulin Secretion and Insulin Sensitivity at Different Stages of Glucose Tolerance: A Cross-Sectional Study of Japanese Type 2 Diabetes

M. Fukushima, M. Usami, M. Ikeda, Y. Nakai, A. Taniguchi, T. Matsuura, H. Suzuki, T. Kurose, Y. Yamada, and Y. Seino

To evaluate the factors causing glucose intolerance in type 2 diabetes in Japan, insulin secretion and insulin sensitivity were compared across the range of glucose tolerance. Subjects were divided into 3 groups: normal glucose tolerance (NGT), impaired glucose tolerance (IGT), and type 2 diabetes (DM) according to the criteria of the World Health Organization (WHO). We examined insulin secretion and insulin sensitivity using fasting blood glucose and insulin levels and 75 g oral glucose tolerance test (OGTT). We used homeostasis model assessment (HOMA) β-cell and insulinogenic index (30 minutes) to estimate insulin secretion and HOMA-insulin resistance (IR) and insulin sensitivity index (ISI) composite for insulin sensitivity. Although insulin resistance plays an important role in the development of diabetes in many ethnic populations, the differences in insulin sensitivity between NGT and IGT and between IGT and DM are small in Japanese patients. On the other hand, as glucose intolerance increases, insulin secretion decreases most remarkably both between NGT and IGT and between IGT and DM in Japanese patients. Decreasing insulin secretion and decreasing insulin sensitivity both occur in developing type 2 diabetes in Japanese patients, but decreased basal and early-phase insulin secretion had more pronounced contribution to glucose tolerance than the indices of insulin sensitivity. Japanese type 2 diabetic patients are characterized by a larger decrease in insulin secretion and show less attribution of insulin resistance.

TYPE 2 DIABETES is characterized by both decreased insulin secretion and decreased insulin sensitivity, but the degree of contribution of these 2 factors in the etiology varies.[1,2] Impaired insulin secretion and impaired insulin sensitivity both occur in the development of type 2 diabetes, but the contribution of these factors differs in certain ethnic populations.[3-6] The prevalence of diabetes is increasing in Japan and is now comparable to other countries. However, there are some differences between Japanese and other ethnic populations. The mean body mass index (BMI) of epidemiologic studies of type 2 diabetes in Japanese is around 24, which is lower than the studies of other ethnic populations.[7-11] In previous studies, we have examined insulin secretion and sensitivity using 75 g oral glucose tolerance test (OGTT) and minimal model analysis.[4,12,13] There were some differences in factors responsible for glucose tolerance of Japanese subjects in comparison to the other studies. We have reported that lower insulin secretory capacity in Japanese subjects would be unlikely to compensate for only a slight decrease in insulin sensitivity.[14] However, to understand the profile of Japanese subjects at various stages of glucose tolerance, a large number of subjects had to be examined.

In the present study, we have investigated insulin secretion and insulin sensitivity of 684 Japanese subjects across the range of glucose tolerance: normal glucose tolerance (NGT) (fasting plasma glucose [FPG] level < 6.1 mmol/L and 2-hour plasma glucose [PG] level < 7.8); impaired glucose tolerance (IGT) (FPG level < 7 and 7.8 < 2-hour PG level < 11.1); and type

From the Department of Diabetes and Clinical Nutrition, Graduate School of Medicine, Kyoto University, Kyoto; Division of Diabetes, Ikeda Hospital, Osaka; Division of Diabetes, Kansai-Denryoku Hospital, Osaka; Kansai Health Management Center, Osaka; and the School of Health Sciences, Faculty of Medicine, Kyoto University, Kyoto, Japan.

Submitted January 2, 2003; accepted February 20, 2004.

Supported in part by Grants-in-Aid for Creative Scientific Research (10NP0201) and for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan, by a grant from "Research for the Future" Program of the Japan Society for the Promotion of Science (JSPS-RFTF97I00201), and by Health Sciences Research Grants for Research on Human Genome, Tissue Engineering and Food Biotechnology from the Ministry of Health, Labour and Welfare.

Address reprint requests to Mitsuo Fukushima, MD, PhD, Department of Diabetes and Clinical Nutrition, Graduate School of Medicine, Kyoto University, 54 Kawaharacho, Shogoin, Sakyo-ku, Kyoto 606-8507, Japan.

0026-0495/04/5307-0010$30.00/0

doi:10.1016/j.metabol.2004.02.012

Table 1. Clinical Characteristics of the Subjects With Varing Degrees of Glucose Tolerance

	NGT	IGT	DM
N (M/F)	176 (125/51)	158 (112/46)	350 (248/102)
Age (yr)	49.1 ± 0.9	52.7 ± 0.7*	52.6 ± 0.4*
BMI (kg/m^2)	23.5 ± 0.2	23.9 ± 0.2	24.7 ± 0.2*†
FPG (mmo/L)	5.3 ± 0.03	5.8 ± 0.04*	8.1 ± 0.10*†
2-h PG (mmol/L)	5.9 ± 0.09	9.2 ± 0.08*	15.6 ± 0.23*†
Insulin-0 (μU/mL)	5.1 ± 0.19	5.7 ± 0.23	6.6 ± 0.22*†
Insulin-30	31.3 ± 1.78	24.8 ± 1.32*	15.1 ± 0.61*†
Insulin-60	43.7 ± 2.37	35.5 ± 2.15*	24.2 ± 1.04*†
Insulin-90	45.9 ± 3.76	43.9 ± 3.29	27.4 ± 1.26*†
Insulin-120	32.2 ± 2.03	41.1 ± 2.42*	29.3 ± 1.25†
Triglycerides (mg/dL)	120.4 ± 6.9	190.4 ± 33.5*	191.5 ± 13.5*
Total cholesterol (mg/dL)	205.8 ± 2.9	211.9 ± 3.0	211.4 ± 2.2
HDL-cholesterol (mg/dL)	56.3 ± 1.6	52.3 ± 1.6*	50.8 ± 0.8*

*Significant difference *v* NGT; †significant difference *v* IGT.

2 diabetes (DM) (FPG level ≥ 7 or 2-hour PG level > 11.1).[15] The homeostasis model assessment (HOMA) β-cell and HOMA-insulin resistance (IR) indices calculated by HOMA were used to determine insulin secretion and sensitivity at the fasting state.[16-18] The insulinogenic index (30 minutes) and insulin sensitivity index (ISI) composite were determined by 75 g OGTT.[19-21] We compared these indices across the range of glucose tolerance from normal to type 2 diabetes to evaluate the causative factors.

SUBJECTS AND METHODS

OGTT (75 g) was used to divide 684 Japanese subjects into 3 groups: NGT, IGT, and DM according to the criteria of the World Health Organization (WHO) in 1998.[15] There were 102 isolated IGT subjects (FPG level < 6.1 and 7.8 < 2-hour PG level < 11.1) in 158 IGT subjects. We recruited subjects from Kyoto University Hospital, Ikeda Hospital, Kanai Hospital, Kansai Health Management Center, and Kansai-Denryoku Hospital during 1990 to 2003. The subjects showed no signs of hypertension, hepatic or renal diseases, engaged in no heavy exercise, or took any medications before the study. Blood was drawn in the morning after a 12-hour fast. The plasma glucose was measured by the glucose oxidase method, and serum insulin was measured using 2-site immunoradiometric assay (Insulin Riabead I; Dainabot, 1990-1991 and Insulin Riabead II, Dainabot, 1992-2003, Tokyo, Japan). The assay results of the same samples with these 2 insulin assay methods showed a very high correlation ($r = 0.99$, $P < .0001$) in the usual assay range. The lipid profiles were measured as reported previously.[22]

The indices of basal insulin secretion and sensitivity were evaluated by HOMA and calculated as follows: HOMA-IR = FIRI × FPG/22.5, HOMA β-cell = 20 × FIRI/(FPG-3.5), where FIRI is fasting plasma insulin level(μU/mL) and FPG is fasting plasma glucose levels (mmol/L).[14-16] ISI composite was calculated according to the formula as follows: 10,000/(Glu 0 × Ins 0 × mean Glu 0−120 × mean Ins 0−120)$^{0.5}$.[19] Insulinogenic index (30 minutes) was estimated as follows: (Ins 30 − Ins 0)/(Glu 30 − Glu 0).[20,21]

Statistical Analysis

Statistical analysis was performed with the StatView 5 system (Abacus Concepts, Berkeley, CA). Unpaired student's *t* tests and simple regression analysis were used for the comparisons of clinical parameters. For the analysis of variance, Bonferroni test was used and $P < .05$ was considered significant. We used multiple regression analysis for the comparison of the relationship between area under the curve for glucose (G-AUC) and the indices of insulin secretion and sensitivity. The data are expressed as mean ± SEM.

RESULTS

Table 1 shows the characteristics of the subjects in this study. There was a 3.6-year difference between NGT and IGT, and no significant difference between IGT and DM in age. There was no significant difference between NGT and IGT, and only 0.8 difference between IGT and DM in BMI. The mean values of the HOMA-IR of NGT, IGT, and DM were 1.2, 1.5, and 2.4, respectively, only representing somewhat small differences between each of the groups, as shown in Fig 1A. The mean values of the ISI composite for NGT, IGT, and DM were 8.6, 7.1, and 5.8, respectively, also representing relatively small differences between the 3 groups (Fig 1B). In contrast, there was a dramatic decrease in HOMA β-cell among the 3 groups, as shown in Fig 2A, as there was also in the insulinogenic index, as shown in Fig 2B.

We then examined the relationship between the G-AUC and the indices of insulin secretion and sensitivity. The scattered plots of simple regression analysis between the G-AUC and the 4 indices are presented in Fig 3. There were significant relationships between G-AUC and the 4 indexes. Multiple regression analysis showed that HOMA-IR, HOMA β-cell, ISI composite, and insulinogenic index were independent factors to explain the variability of 60.7% of G-AUC ($P < .0001$). The

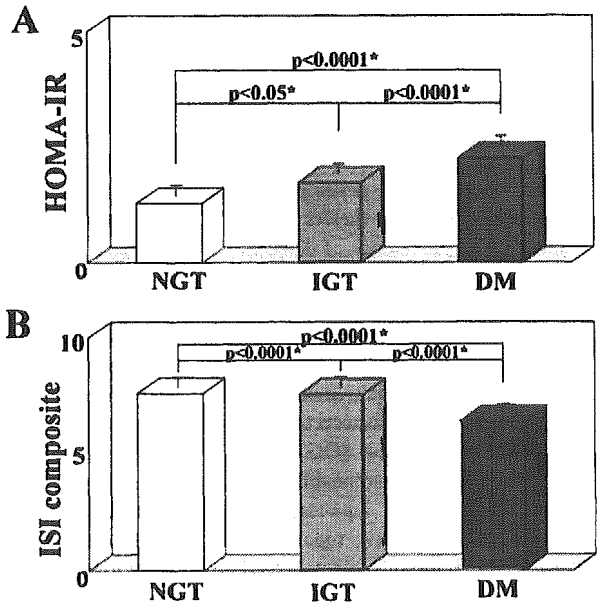

Fig 1. (A) Insulin resistance index at basal state was compared across the range of glucose tolerance. Insulin resistance increases with increasing glucose intolerance, but the differences are relatively small in Japanese subjects. (B) Insulin sensitivity decreases with increasing glucose intolerance according to the ISI composite, and the differences also are relatively small. *Significant differences assessed by analysis of variance.