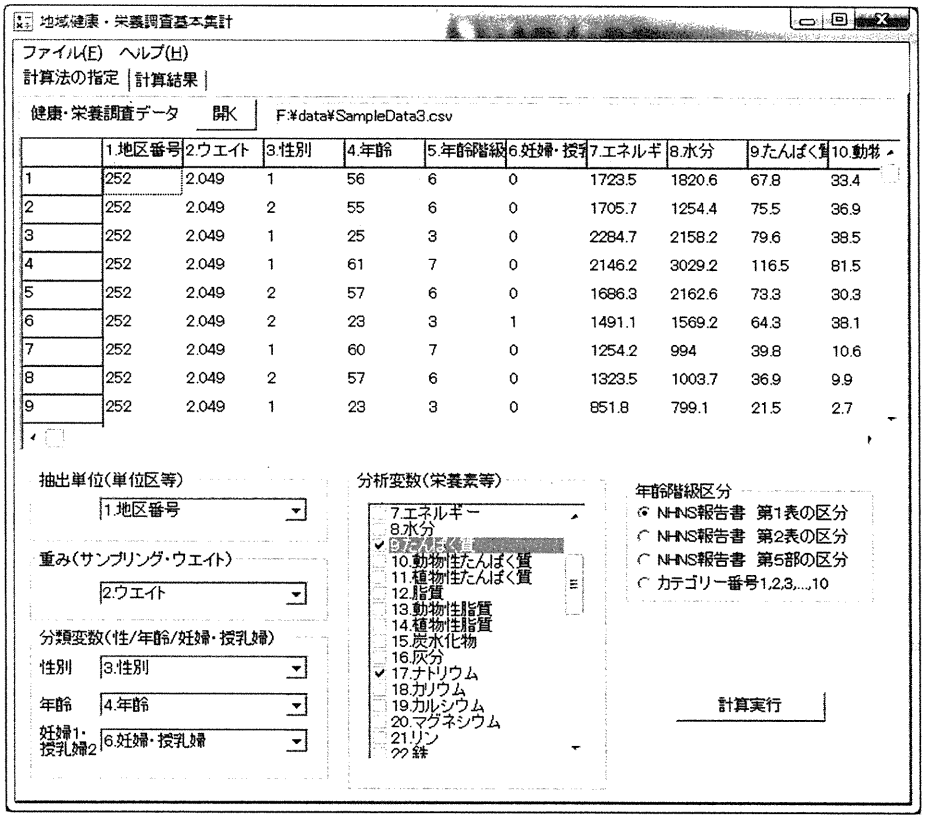
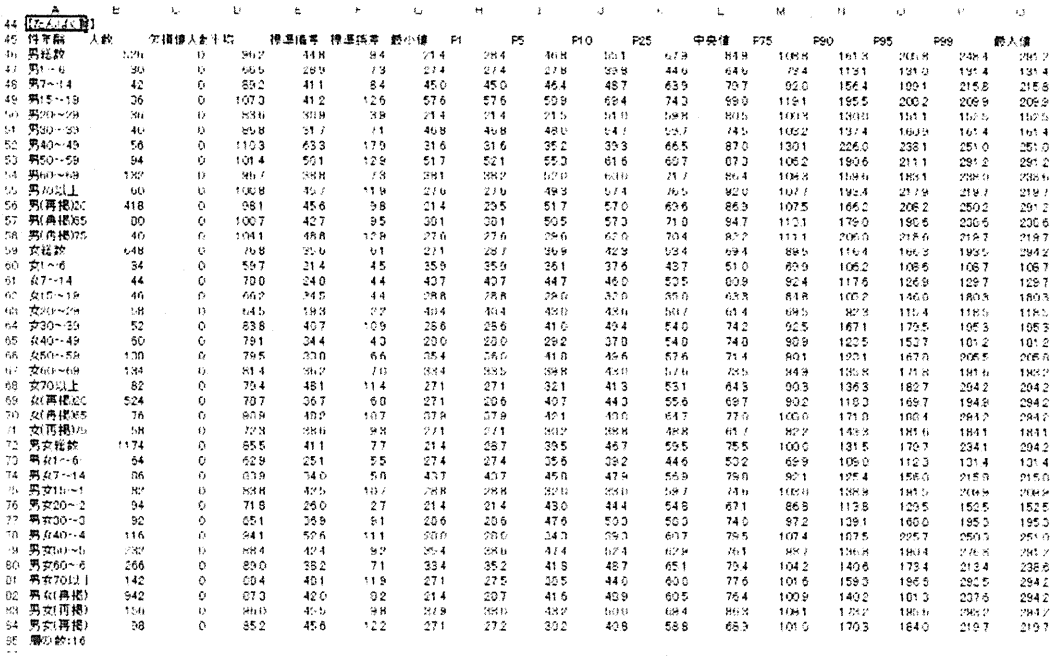
図２．地域健康・栄養調査基本集計ソフトウェア



- クラスター抽出を考慮した誤差計算。単純無作為抽出にも対応。
- サンプリングウェイトを考慮した集計
- 国民健康・栄養調査の第１表、第２表、第５部の年齢区分に対応。独自年齢区分も可。
- インターネット上で公開。

（計算結果例）



分担研究報告書

平成23年度厚生労働科学研究費補助金
「健康増進施策推進・評価のための健康・栄養モニタリングシステムの構築」

「健康増進施策推進・評価のための健康・栄養調査データ活用マニュアル」の構築

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研究要旨

都道府県健康・栄養調査データを健康増進施策の評価に有効活用することを目的として、これまでに検討・蓄積したデータ及びツール、並びに国立保健医療科学院で実施されてきた研修での経験等を踏まえて、都道府県・政令市並びに保健所等の実務者を主なターゲットとしたマニュアルを作成した。

現場のニーズに沿った実用的な内容とするために、2011年9月に全国の都道府県から約20名の参加を得てワークショップを開催し、マニュアルや今後必要な取組などについての意見を求めた。また、国では、健康日本２１の最終評価作業が行われている時期であり、関連する最新の情報をマニュアルに含めた。2011年11月に「健康増進施策推進・評価のための健康・栄養調査データ活用マニュアル」を完成させ、全都道府県・政令市に提供した（http://www.nih.go.jp/eiken/chosa/pdf/20111215.pdf）。

各都道府県においては、健康増進計画（健康日本２１地方計画）の最終評価を行う時期であり、本マニュアルが活用されるとともに、2012年2月に国立保健医療科学院で行われた「健康・栄養調査の企画・運営・評価に関する研修」での教材として使用された。今後、調査データをより有効に活用するためには、人材の育成も含めた体制を、それぞれの地域（都道府県）で構築していくことが必要と考える。

A．目　的

都道府県の健康増進計画の評価や、新たな計画策定に際しては、中長期的な視点から健康・栄養調査データを活用し、適切な解釈を行うことが必要である。そこで、本研究班の成果物の一つとして、都道府県・政令市並びに保健所等の実務者向けのマニュアルを作成し、提供することを、最終年度の課題とした。

B．方　法

（1）現場の状況及びニーズの把握

2011年5月に各都道府県・政令市の栄養主管部局に今回のマニュアルの作成趣旨とマニュアルを作成するためのワークショップの開催について連絡した。2011年9月に「健康増進施策推進・評価のための健康・栄養調査データ活用マニュアル（仮題）」の作成にむけた研修会（ワークショップ）を主催した（表1）。そこで、本マニュアルの一次原稿を配布するとともに、下記の内容の講義及びグループワークを行い、参加者からの意見（その後のメールによるフィードバックを含む）をとりまとめた。その際、都道府県健康増進計画の策定・評価と健康・栄養調査について、現場が抱える課題やそれに対する解決方策、並びに望まれる支援等に関する事項を論点として示した。

表１

「健康増進施策推進・評価のための健康・栄養調査データ活用マニュアル（仮題）」の作成にむけた研修会（ワークショップ）

日時：平成23年9月2日（金）10:30～16:00
場所：大阪市立大学文化交流センター
内容：
1. 開催の挨拶・趣旨説明　吉池信男
2. マニュアル（案）に沿ったミニレクチャー（Part Ⅰ）
   a. 国民健康・栄養調査の意義と課題　（西　信雄）
   b. データ活用の視点にたった都道府県調査の設計と実施　（横山　徹爾）
   c. 都道府県健康・栄養調査のデータ蓄積と活用（吉池信男）
3. 都道府県等における取組事例
   ・熊本県における県民健康・栄養調査の活用について（久保彰子）
   ・長野県における健康・栄養調査及び計画評価へのデータ活用　（小林真琴）
4. マニュアル（案）に沿ったミニレクチャー（Part Ⅱ）
   d. 都道府県調査データの解析と施策評価への活用（横山徹爾）
   e. 市町村と連携した調査の実施とデータの活用　（由田克士）
5. グループワーク：健康日本21の最終評価にむけた調査データの活用
6. マニュアルに対する要望、意見交換
7. 総合討論、まとめ

（２）マニュアルの作成と公開

（１）の結果を踏まえて、マニュアル構成及び内容を、本分担研究課題の研究分担者及び研究協力者が検討し、マニュアルを作成した。作成したマニュアルは、全都道府県・政令市に郵送で送付するとともに、pdf 版を国立健康・栄養研究所のホームページにアップロードした。

C．結　果

（１）現場の状況及びニーズの把握

ワークショップ及びその後メールで出された意見等を以下にまとめた。

【1】最終評価におけるデータ活用上の問題点・実情など

（「→」以下は、上記についての「対処の現状」）

1. 調査の実施において

・国民健康・栄養調査自体知られていない
・地域間で協力率が異なる
・協力率を上げる（n 数を増やす）ことは困難であり、そのための負担が大きい
→高齢者の食物摂取状況調査票の記入は、別途簡単な様式を作成し、記入後のものから本調査票に転記している
・直接会えない方のデータは信頼性が低いと考える
・高齢者の場合は、生活習慣調査票の聞き取りを行っている
◆直接の聞き取り－身体状況調査時の送迎・夜間訪問・手紙も（マンション等の住人へのコンタクトや連絡先の把握は難しい）
・調査員の説明状況がどの程度か把握しきれない

2. 都道府県における国民健康・栄養調査データの活用について

・毎年集計・解析・まとめを活用している
・比較しづらい
→同様の報告書様式にしている
・n数が限られているので、評価困難（特に子ども・若い世代）
・複数年のデータを積み上げて経年的に評価するなどデータの有効かつ適切な活用方法を検討する必要がある
・長期的な保存を考えるとデータ保存ができず毎年申請するのは現実的でない

3. 都道府県健康・栄養調査におけるデータの活用に関して

・（他県他市と）比較しづらい、n 数が少ない
・過去のデータが活用できる状態で残っていない
・不安・問題だが全体のn数が少ないデータを活用
・市町村では、十分調査を行える体制でない場合があるなど独自に栄養摂取状況調査等を実施することは困難
・定期的（例えば５年毎）に実施している場合、健康増進計画や食育推進計画の立案に必ずしも最新の結果を利用できない
・自治体独自で得られたデータが、健康増進施策の立案や評価に活用されていないケースがある
・調査票情報提供データは破棄・消去が必要なので、その都度申請
→手持ち資料としてでも良いので、目標項目について解析したデータを持っておけるよう部署内で検討する予定
→経年で比較
→県民意識調査データ、過去の重点項目の内容と比較
→評価の方針をワーキンググループで決め、ベースライン調査と同じ調査を行う（設問を過去同様にし対応）以外対応できない
→県と比較できるよう生活習慣調査（アンケート）の調査票・調査結果を市町にも配布
→アンケート調査の上乗せ
→別途アンケート等独自調査（若い世代のみなど）を実施・活用
→学校保健統計（ただし野菜の摂取量などは把握できない）・食育計画用のアンケートなど他の調査を活用
→母子手帳発行時に簡単な質問をし、それを活用

4. その他計画立案・集計・解析・評価等に関して

・統計的な評価ができていない（平均のみしか出ていない）
・調査設計段階で、協力率を考慮した標本数を設定しても性・年齢階級までは想定できない
・どのようにすればよいのか不安なまま進めている
・健康増進計画の目標値に県健康・栄養調査の結果を使っているが、データ解析が不十分
・今ある材料で検討せざるを得えない所も多いのではないかまた、その場合の数字の独り歩き・誤った結論になりかねないことが危惧される
・「標準誤差や信頼区間をつけて評価する必要までないのでは？」との意見もある
・財政状況が厳しい中、継続して予算を確保すること、人事異動の範囲が公衆衛生部門に限られない中で、誰が担当しても調査の精度や計画評価の作業に「一定の質」を担保することにとても苦慮する
・血液検査の結果を分析で利用していなかったため県民健康・栄養調査から血液検査項目が削除されてしまった
・県の総合計画上で、指標について評価結果を毎年公表できるように「健康・栄養調査を毎年実施する」という話しが浮上したが、一転して「毎年把握できないような指標は削除」になった
・計画評価を行う部署にデータの適切な活用や分析方法・検定などについて説明できる人材が少ない（担当部署で説明できない分析結果は、未公表あるいは積極的に PR されない）
・H24 年度中に作成する健康増進計画の値をH24 年秋～冬（H23 年分の国調データ）くらいまで待って、国からもらい作業を始めるといったタイトなスケジュールで実施せざるを得ない
・計画作成を片手間でやっているような状況もある
・若い栄養士のスキルが高くない
・人員増など体制整備の見込みがない
・市町栄養士の配置がなかなか進まない
→市町村の連携
→調査委員会招聘の先生の協力
→休日返上での点検作業
→調査票の点検や集計の見直しにかかる労力や時間に対し誰からも理解が得られなくても「折れない心」を担当者が持つ

5. 関係機関（者）間の連携・共通認識に関して

・県の調査の検討委員会と「健康日本21」の評価の委員会が連動していない
・「連携」は、話としては理解できるが、現状とのギャップを感じる
・地域課題の把握の必要性を十分認識していないように感じる
・ポピュレーションアプローチとハイリスクアプローチの必要性が認識されていないあるいは知識がない
・声をかけても実務に追われていて断られたり、国民健康・栄養調査を保健所として受けること（他職種の協力を得ること）自体厳しい現状がある

6. 外部機関（管理栄養士養成機関・教育委員会など）との連携・関係構築

・下記のようなことの相談・依頼先（公衆衛生の専門家・機関など）がない
◆調査の企画・評価・結果のデータ解析
◆健康増進計画評価への活用
◆食品成分表の改訂等により単純比較できない過去のデータとの比較方法
◆結果公表における、わかりやすさや誤解の無いような伝え方・表現
◆結果用に把握するものとしての天候・地震・歴史的な事柄
◆国民健康・栄養調査データを複数年まとめて集計する場合、郵送法によるアンケート調査・頻度調査などを行う際の限界や活用できない理由など

【2】解決につながる今後の対応・方策・提案・要望など

1.「健康増進施策推進・評価のための健康・栄養調査データ活用マニュアル」に関連して

・上記マニュアルが完成したら、各都道府県やブロックごとなどで研修会を開いたほうが良い
・予算確保・評価に対応できる内容の資料など必要な情報（下記）等の一括提供とそれらの周知徹底
◆「都道府県健康・栄養調査マニュアル」等の関連資料
◆技術支援ソフト
◆国立保健医療科学院の研修に関する案内
◆評価に耐えうる数値を国レベルの調査から入手できない場合は、独自調査によって健康度を把握することが「必要」（「望ましい」ではない）ということを明記したものなど
・確認するだけで必要な項目がそのまま使えると作業効率が上がるので、実例を多く提供して欲しい
・市町栄養士と共に学ぶテキストにも活用したい

2. 健康増進施策推進・評価のための健康・栄養モニタリングシステムについて

・とても役に立つツールなので、データベースの更新を継続して欲しい

3. 上記以外の資料提供について

・ハンドブックとして下記資料を1冊にまとめたものが欲しい
◆平成16年「地域における健康・栄養調査の進め方」
◆都道府県健康・栄養調査マニュアル
◆「健康増進施策推進・評価のための健康・栄養調査データ活用マニュアル」からの抜粋で「健康増進施策推進・評価のための健康・栄養モニタリングシステム」データベースとデータの連続性についての部分

◆国立保健医療科学院等の各種研修での調査設計～データ解析・評価など
・調査の変遷を(項目や内容の変更なども含め)時系列的に整理したものも欲しい

4. 都道府県における国民健康・栄養調査データの活用について

・予算確保・評価に対応できる内容の資料(◆データ入手のための申請方法◆必要な書類の様式等)や情報の一括提供
・結果データをもう少し早く出していただきたい
・都道府県等で、健康・栄養調査の一部として活用する場合は永年あるいは長期使用できる、というシステムにできないのか
・厚生労働省が必ず入れる項目(設問内容)や評価の例を示して欲しい
・世帯の中の家族関係(夫婦か親子かなど)を把握しやすくできないか

5. 都道府県健康・栄養調査等のデータの活用に関して

・全国共通の内容・形式にすべき
・調査内容や方法を変える(1日→2日に増やす)
・調査データの解析が重要
・データの管理を厳密にするために通知等で、エクセル等シート様式の提示など何らかの拘束が必要
・過去の調査の継続(データの保管管理)
・調査の精度と実際に見込める改善の度合い、改善が見込める期間など根拠ある指標を明確に設定し、評価の計画も示す
・健診データの活用
・評価をふまえて予算取りし、事業を立ちあげる
・何年に1回か必ず行政予算を取るようにする
・担当部署の中に「説明できるほど理解している」人を増やす
・人員増など体制整備

6. 情報提供に際して

・提供情報は一目でわかるような表現で
例 1)HP アドレスを示す際に日本語でも「●●ホームページ」などと書く
・注意深く見ずに、少ないデータ数での結果を市町に下ろしてミスリードさせないようにしてほしい

7. 関係機関(者)間の連携・共通認識事項など

・国民健康・栄養調査の意義がしっかり認識できるようにすること、調査や評価を実施するにあたって研修を受けることは必須
・"必要性"についての意識啓発と実施
(保健所も市町村も担当者や行政栄養士に限らず、公衆衛生関係者全員が、充分に認識し、共通理解を持ち方向性を揃える)
◆ポピュレーションアプローチとハイリスクアプローチ
◆適切な評価・分析
などについて
・統計精度などの一連の流れを関係者間で共有する

8. 外部機関(管理栄養士養成機関・教育委員会など)との連携・関係構築

・専門家(学識経験者等)や相談窓口の配置・設置とその周知
・国立保健医療科学院の専門コースを復活して欲しい
・研修会等は、直近の業務に反映できる配慮を
例)国立保健医療科学院の研修は、予算要求の時期との関係等から年度初めの夏頃までになど
・中堅の人材に対する研修やフォロー研修を実施して欲しい
・今後も研修会等を継続して欲しい

【3】その他の意見・要望など

・国勢調査のようにCMなどを活用し、国民健康・栄養調査の認知度をアップさせる(経費の問題もあるが)
・国立保健医療科学院公開の技術支援ソフトで、高度な集計や分析結果が出せる環境になった
・◆健康増進施策推進・評価のための健康・栄養モニタリングシステム◆上記の技術支援ソフト◆それらに伴う公開参考資料等については、広く知られておらず、まだ十分活用されていない
・「健康増進施策推進・評価のための健康・栄養モニタリングシステム」のような実践的ツールがあると
◆作業効率が上がる　◆予算取りしやすい
・仕様書は、業者に委託する際にもとても重宝なので、他の調査にもすぐ使ってみたい
・国立保健医療科学院で実施されている健康栄養調査の研修内容は、一貫した積み上げの仕事によるものと感じる

(2) マニュアルの作成と公開

マニュアルの構成内容を表2に示す。国では、健康日本21の最終評価作業が行われている時期であり、関連する最新の情報をマニュアルに含めた。なお、マニュアルの内容は、本研究班の「平成 21 年度～23 年度総合研究報告書」の資料として掲載した。

http://www.nih.go.jp/eiken/chosa/pdf/20111215.pdf からダウンロード可能である。

D. 考 察

これまで本研究班で検討・蓄積したデータ及びツール、並びに国立保健医療科学院で実施さ

れてきた研修での経験等を踏まえて、都道府県・政令市並びに保健所等の実務者を主なターゲットとしたマニュアルを作成した。その際、ワークショップ等の機会を通じて、都道府県等の担当者から意見聴取や情報共有を行ったことは、本マニュアルを活用しやすいものとするために有用であったと考える。

ワークショップの機会に得られた意見等（前述）は、今後、都道府県等における健康増進施策の推進基盤となる健康・栄養モニタリングシステムを改善・強化させるために、有用な情報である。しかし、今回マニュアルを作成し、技術的な面での情報やツールの提供を図っても、その必要性が意思決定者等に認めてもらえない、あるいは人材が配置されていない、必要な研修機会がない（身近に指導者がいない）等の課題が阻害要因として指摘された。例えば、本マニュアル及び提供した関連ツールについて、すべての者が独習することの可能なレベルに到達しているとは言いがたい。しかし、国立保健医療科学院で毎年２月に実施されている４日間の研修に参加できる者は限られている。

実際に調査データを処理・解析する際には、身近に指導者（助言者）がいることが理想的である。現在さらに数が増えている管理栄養士養成校には、公衆衛生や公衆栄養等の担当教員が必ずおり、大学院を有しているところも少なくない。大学院の科目（外部聴講による履修も可能）に、本マニュアルやツールをつかった演習を取り入れることを含め、管理栄養士養成校を、地域（都道府県など）のリソースとして有効に活用することが、今後重要になると思われる。

E. 結　論（まとめ）

都道府県健康・栄養調査データを健康増進施策の評価に有効活用することを目的として、都道府県・政令市並びに保健所等の実務者を主なターゲットとしたマニュアルを作成した。各都道府県においては、健康増進計画（健康日本２１地方計画）の最終評価を行う時期であり、さっそく、本マニュアルが活用されている。今後、調査データをより有効に活用するためには、人材の育成も含めた体制を、それぞれの地域（都道府県など）で構築していくことが必要と考える。

F. 研究発表

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G. 知的所有権の取得状況

なし

表２　「健康増進施策推進・評価のための健康・栄養調査データ活用マニュアル」の構成内容

＜目次＞

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population, 27 patients with moderate or severe SEC had restoration of sinus rhythm without complications.

The use of 2-phase MDCT with the analysis of late-phase images can improve the specificity of scan in distinguish severe SEC from thrombus [14]; nevertheless, the use of additional late-phase images caused a significant increase in radiation exposure.

On the other hand, in multilobated LAA or in cases with severe SEC, also MTEE may miss the presence of thrombosis [15–17]. Therefore, in clinical practice, the detection of thrombosis at MDCT, even though MTEE is negative, may induce the treating physician to postpone subsequent procedures. In patients without atrial thrombosis at MTEE, no embolic events occurred after transcatether procedures and CV, supporting the accuracy of MTEE and the lower specificity of MDCT. The poor PPV of MDCT and the excellent outcome free from embolic events in negative MTEE confirm the crucial role of echocardiography in the management of patients with atrial fibrillation [18].

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Accumulation of cardiovascular risks in Japanese women with abnormal glucose and mild to moderate hypercholesterolemia

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To the editor:

Women have a lower incidence of cardiovascular disease (CVD) compared to men until they reach menopause, then the incidence of CVD increases and becomes similar to that of men, and increases with age [1]. Some theories for this lag in the development of CVD in women include unfavorable changes in lipid profiles in relation to hormone deficiency due to post-menopause [2]. Abnormal glucose, including diabetes (DM) and impaired glucose tolerance, is an established risk factor for CVD, and its influence on the development of CVD is greater in women than men [3]. Further, women with DM, compared to men, have a higher rate of overall morbidity and mortality after their initial ischemic CVD event [4].

The MEGA Study is a first and solitary large-scale primary prevention study conducted in Asia to investigate the effect of pravastatin treatment in mild to moderate hypercholesterolemic Japanese, which was published in 2005 [5]. This study included a number of women [5], hence we aimed to figure out the risk profile of hypercholesterolemic

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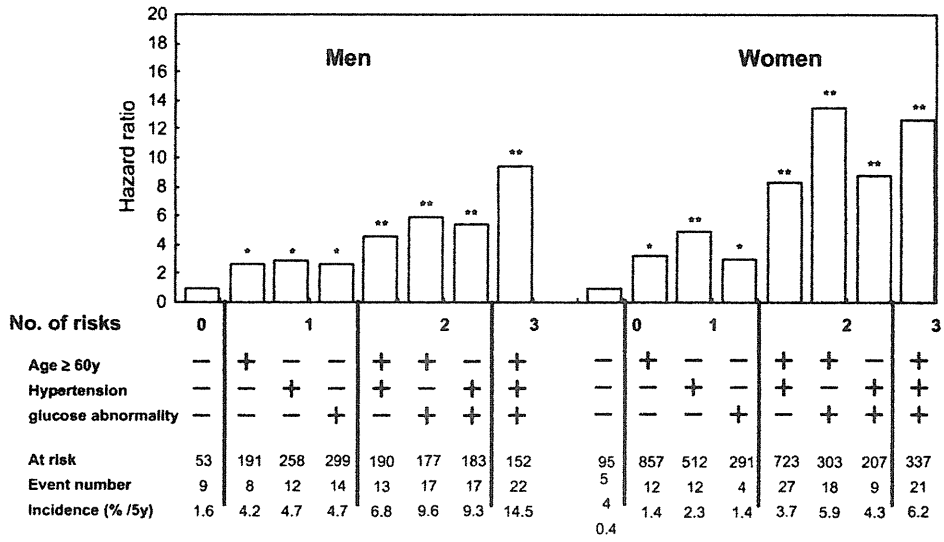

Fig. 1. The accumulation of risks for cardiovascular events in hypercholesterolemic men and hypercholesterolemic post-menopausal women in Japan. Hypertension was reported by physicians, and abnormal glucose was defined by fasting plasma glucose ≥6.1 mmoL/L or under anti-diabetic agents. Asterisks indicates $p<0.01$ (**) and 0.05 (*).

women with abnormal glucose in the present study. The 7832 patients with mild to moderate hypercholesterolemia with no history of CVD were allocated to diet alone or diet plus pravastatin (10–20 mg daily, the approved dose in Japan), and followed for an average of 5 years, and a significant 27% risk reduction of CVD was found in the diet plus pravastatin group in main analysis of the MEGA Study [5].

The present study included 5356 women of whom 1296 had abnormal glucose (952 established DM, 344 impaired fasting glucose), and 2476 men of whom 914 had abnormal glucose (680 established DM, 234 impaired fasting glucose) in the MEGA Study.

The women with abnormal glucose in comparison to women without were older (≥60 years old, 56% vs. 51%, $p=0.004$), had a higher rate of hypertension (47% vs. 41%, $p=0.001$), higher LDL cholesterol (LDL-C) (4.13 vs. 4.08 mmol/L, $p=0.001$), and lower HDL-C (1.48 vs. 1.57 mmol/L, $p<0.001$). This trend is similar to men, but women with abnormal glucose had higher rate of hypertension than men with abnormal glucose (47.1 vs. 41.9%, $p=0.01$).

The hazard ratio (HR) and its 95% confidence interval (CI) calculated by using Cox's proportional hazard model adjusting for age and treatment arm for coronary heart disease (CHD: myocardial infarction, angina, revascularization, sudden/cardiac death), stroke and any CVD in women with abnormal glucose in comparison to those with normal glucose were 3.6 (95% CI, 2.2–6.0; events/patients, 28/4060 vs. 34/1296), 1.3 (0.7–2.4; 37/4060 vs. 16/1296) and 2.4 (1.7–3.4; 70/4060 vs. 55/1296), respectively. The corresponding values in men were 2.8 (1.8–4.5; 29/1562 vs. 51/914), 1.5 (0.8–2.7; 23/1562 vs. 23/914), and 2.3 (1.6–3.3; 53/1562 vs. 77/914). This indicates that women with abnormal glucose may be at greater risk for CHD than for stroke compared to men, although there was no significant sex interaction ($p=0.39$).

Subsequently, the HR and its 95% CI adjusting for treatment arm for any CV events in men with abnormal glucose alone, abnormal glucose plus hypertension or older age (≥60 years old), and abnormal glucose plus hypertension plus older age were 2.7 (1.2–6.2), 5.4 (2.4–12.2), 5.9 (2.6–13.3) and 9.4 (4.3–20.5) in comparison to that in men without any risk factor (Fig. 1). The corresponding values in women were 3.0 (0.7–11.9), 8.8 (2.7–28.6), 13.5 (4.6–39.8) and 12.7 (4.3–37.2), indicating that the risk of CV increased more markedly among hypercholesterolemic women with abnormal glucose than men, when aging and/or hypertension is overlapped. However, we could not show statistical significant sex interaction effects of these findings.

Interestingly, the absolute risk of CVD is one-third to one-half lower in women than in men with abnormal glucose and hypercholesterolemia, whether or not they had additional risk factors. The relative risk of CVD in women with two risk factors was almost equal to or greater than men with one risk factor. Nevertheless, hypercholesterolemic women with more than two risk factors among aging, abnormal glucose and hypertension should receive aggressive preventive treatment of CVD, because their risk is around 5% per 5 years or higher and further women have a worse prognosis after suffering an initial CVD event.

In patients with DM, lipid management with a statin is well-established in clinical trials to reduce CVD risk; thus statins should be the cornerstone of treatment in this population [6]. A previous post-hoc analysis from the MEGA Study showed that pravastatin markedly reduced the risk of ischemic disease in hypercholesterolemic women ≥60 years old (HR 0.50, $p=0.007$) [7]. However, a multi-pronged treatment approach is clearly needed in this population, as reinforced by our finding in this analysis that despite effective statin treatment, too many CVD events still occurred in this higher-risk group.

An important limitation to our findings is the low incidence of CVD events in the MEGA Study, especially for women, since it was conducted in Japan which has low burden of the CVD compared to most of other countries. In this analysis, we have merged people with DM and impaired fasting glucose as abnormal glucose to increase statistical power. As previously reported [8], people with abnormal glucose had a significantly increased risk of CVD than those with normal fasting glucose. However, building the evidence base in women, including those with glucose abnormality, for their risk and effective treatment is important to establish optimal treatment strategies.

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The Authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [9].

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Lipid-soluble vitamin C palmitate and protection of human high-density lipoprotein from hypochlorite-mediated oxidation

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During exposure to pro-inflammatory hypochlorous acid (hypochlorite) [1], activity of paraoxonase-1 (PON1), a cardio-protective enzyme [2], is lost from high-density lipoprotein (HDL) [3]. Although vitamin C is an important antioxidant [4], our prior studies indicate only a moderate ability to prevent hypochlorite-mediated loss of PON1 activity [5]. Interestingly, vitamin C palmitate (VCP), a lipid-soluble form, integrates into human erythrocyte membranes and prevents oxidant damage [6]. The purpose of this study was to determine if VCP could similarly protect HDL from hypochlorite-mediated oxidation and loss of PON1 activity.

HDL was isolated from pooled normal human plasma (US Biological, Swampscott, MA) by ultracentrifugation. The use of human plasma was reviewed by Midwestern University's Institutional Review Board and deemed to fulfill the criteria for being exempt from needing approval. HDL (2 mg protein/ml) was incubated at 37 °C either without (control) or with VCP (500 μM, dissolved in ethanol) for 60 minutes; subsequent overnight dialysis removed VCP not associated with the HDL. Following this pretreatment, HDL was exposed to (sodium) hypochlorite (0.3 M) for 90 minutes. Oxidation (chlorination) of HDL was assessed by measuring chloramine accumulation. PON1's physiological lactonase and promiscuous phosphotriesterase and arylesterase activities were measured spectrophotometrically. All these procedures have been described in detail previously [5].

Chlorination of HDL declined from 31 ± 3% of maximum for control HDL to 14 ± 1% of maximum for VCP-treated HDL ($P<0.01$; Fig. 1A). This antioxidant effect indicates that at least some was successfully incorporated into the lipoprotein. Despite this, however, no protective effect of VCP against loss of PON1 enzyme activities was found (Fig. 1B–D).

The decreased chlorination observed in VCP-treated HDL is consistent with the known ability of vitamin C to scavenge hypochlorite [7] and protect low-density lipoprotein from atherogenic modification by hypochlorite [8]. However although VCP's observed inability to prevent loss of PON1 activity might initially seem at odds with this antioxidant effect, it is not inconsistent with at least some prior studies. Others have also reported that, even under conditions where VCP displays antioxidant activity, the overall biological effect may not be beneficial. Thus, similar to the results reported herein, Lee et al. [9] noted an antioxidant ability of VCP to scavenge reactive oxygen species in cultured epithelial cells treated with hydrogen peroxide. However, VCP failed to prevent the inhibition of intracellular communication seen in these cells, but, instead, somewhat enhanced it. In another study [10], although low concentrations of VCP prevented ultraviolet-B-induced formation of reactive oxygen species in cultured keratinocytes, oxidation of the lipid moiety of VCP caused cytotoxicity. Finally, it was recently reported that although vitamin E, a naturally occurring lipid-soluble antioxidant, can protect other lipoproteins from oxidation, its incorporation into HDL actually promotes its oxidation [11]. In another recent study, it was also reported that, under certain (genetic) conditions, vitamin E is ineffective in protecting HDL from oxidation and loss of functionality [12]. Thus, the possible roles of lipid-soluble antioxidant compounds, such as VCP, in protecting HDL from oxidative damage and dysfunction remain unresolved. In conclusion, although VCP protected HDL from oxidation (chlorination) by hypochlorite, cardio-protective PON1 activity still declined. These observations suggest PON1 may be exquisitely sensitive to inactivation during inflammation.

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Research Article Open Access

Assessment of Cholesterol Absorption and Synthesis in Japanese Patients with Type-2 Diabetes and Lipid-Lowering Effect of Ezetimibe

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Abstract

Aims: Cholesterol absorption is reported as an independent risk factor for cardiovascular disease. However, factors related to cholesterol absorption have not been fully examined in patients with type-2 diabetes (T2DM). The aim of this study was to assess cholesterol absorption/synthesis markers and the effect of an inhibitor of cholesterol absorption, ezetimibe, in patients with T2DM with hyper-low-density lipoprotein cholesterolemia.

Methods: We included 59 patients treated with statins (S group) and 121 patients who were not receiving any lipid-lowering treatments (N group). Levels of cholesterol absorption and synthesis markers were compared between the 2 groups and between subjects in the N group with and without microvascular complications. The lipid-lowering effect of ezetimibe treatment (10 mg/day for 12 weeks) was examined in 70 patients with high levels of low-density lipoprotein-cholesterol (LDL-C). These patients were divided into the monotherapy (M) group (n = 57; ezetimibe treatment only) and the combination therapy (C) group (n = 13; ezetimibe and statin treatment).

Results: The levels of cholesterol absorption and synthesis markers were higher and lower, respectively, in patients in the S group than in the N group (both $p < 0.05$). In the N group, the cholesterol-absorption marker levels were higher in patients with microvascular complications than in those without ($p < 0.05$). Ezetimibe decreased total cholesterol and LDL-C levels by 13% and 21% and 11% and 16% in patients in the M group and C group, respectively (all $p < 0.05$). In patients of the M group, ezetimibe decreased the levels of remnant-like particle-cholesterol, high-sensitivity c-reactive protein, and triglycerides (TG; only in cases with TG ≥ 150 mg/dL) by 16%, 5%, and 21%, respectively, and increased high-density lipoprotein-cholesterol by 6.8% (all p 0.05).

Conclusions: Ezetimibe may be a useful therapeutic option to prevent micro- and macrovascular complications for dyslipidemia in patients with T2DM.

Keywords: Cholesterol absorption; Cholesterol synthesis; Cholesterol absorption inhibitor; Type-2 diabetes; Microvascular complications

Abbreviations: A1C: Hemoglobin A_{1C}; BMI: Body Mass Index; CPR: C-Peptide Reactivity; CVD: Cardiovascular Diseases; DM: Diabetes; FBG: Fasting Blood Glucose; HDL-C: High-Density Lipoprotein-Cholesterol; hs-CRP: High-Sensitivity C-Reactive Protein; JDCS: Japan Diabetes Complications Study; LDL-C: Low-density Lipoprotein-Cholesterol; NGSP: National Glycosylated Standard Program; NPC1L1: Niemann-Pick C1-Like 1; RLP-C: Remnant-Like Particle-Cholesterol; TC: Total Cholesterol; TG: Triglycerides; T2DM: Type-2 Diabetes Mellitus

Introduction

A westernized diet has led to an increased cholesterol intake and high morbidity associated with dyslipidemia among the modern Japanese population [1,2]. The Japan Diabetes Complication Study has shown that low-density lipoprotein-cholesterol (LDL-C) is an established risk factor for cardiovascular diseases (CVD), and the risk of CVD increased markedly when abnormal glucose levels and dyslipidemia coexist [3]. Various large-scale clinical trials have shown the beneficial effects of LDL-C-lowering therapy for preventing coronary heart diseases [4,5], and the Japan Atherosclerosis Society has documented a target level for LDL-C in its guidelines for the prevention of atherosclerotic CVD [6]. The guidelines recommend changes in lifestyle by diet and exercise as the first line of therapy in the primary prevention of CVD. However, maintaining changes in lifestyle is difficult, and in some patients, LDL-C levels are not sufficiently decreased [7].

Statins are 3-hydroxy-3-methyl-glutaryl-Coenzyme A (HMG-CoA) reductase inhibitors, which inhibit hepatic cholesterol synthesis and are used as main lipid-lowering agents [8]. However, drugs that alter cholesterol absorption have recently attracted attention after the approval of ezetimibe, which is a selectively inhibits cholesterol absorption from the small intestine [9]. In addition, Niemann-Pick C1-like 1 (NPC1L1), which plays an important role in cholesterol absorption, has been cloned [10]. Limited data has shown that *NPC1L1* gene expression was greater in patients with type-2 diabetes mellitus (T2DM) than in non-DM patients [11]. Because it is controversial whether cholesterol absorption is higher in patients with T2DM than in non-DM patients [11,12] and factors related to cholesterol absorption have not been fully examined in T2DM, we assessed the relationship between cholesterol absorption markers and the clinical characteristics of patients with T2DM. Furthermore, the lipid-lowering effect of ezetimibe [9], a selective cholesterol absorption inhibitor, was evaluated in patients with hyper-LDL-cholesterolemia whose LDL-C

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levels had not reached the target level [6] despite diet or administration of statins.

Patients and Methods

The flow diagram of this study is shown in Figure 1.

Study subjects

The study comprised 180 patients (123 men) with T2DM who had been followed at the Diabetes Center of Tokyo Women's Medical University Hospital for 4 weeks or longer at the time of enrollment (February 2008 to April 2009) and who gave a written informed consent to participate in the study. All patients had hemoglobin-A_{1C} levels (A1C) <10.4% at baseline with a variation of <2.0% during the prior three months. Patients who had hepatic or renal dysfunction, familial hypercholesterolemia, drug-induced/secondary hyperlipidemia, or who were pregnant or nursing were excluded from the study. All patients were classified into two groups: patients not receiving any lipid-lowering treatments (n = 121; no treatment (N) group) and patients treated by statins alone (n = 59; statin-treatment (S) group).

Ezetimibe was administrated at a dose of 10 mg once daily during 12 weeks in 70 patients whose LDL-C levels had not reached the target level

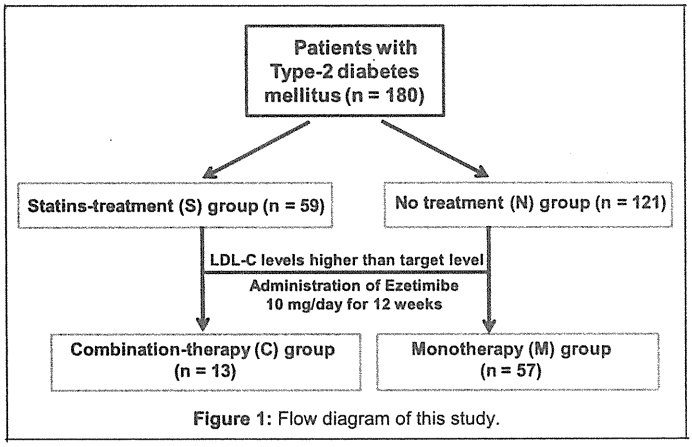

Figure 1: Flow diagram of this study.

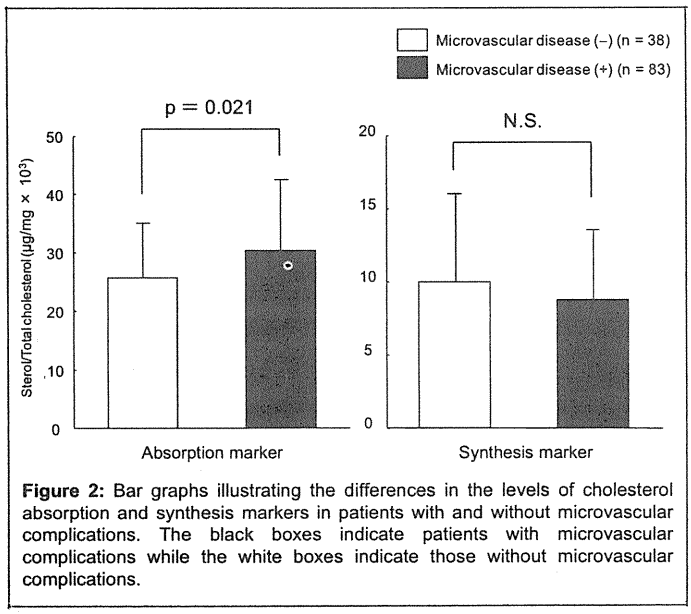

Figure 2: Bar graphs illustrating the differences in the levels of cholesterol absorption and synthesis markers in patients with and without microvascular complications. The black boxes indicate patients with microvascular complications while the white boxes indicate those without microvascular complications.

established by the guidelines of the Japan Atherosclerosis Society [6]: <120 (100) mg/dL in patients without (with) a past history of coronary heart disease. In cases where ezetimibe treatment was added to statin treatment (S group), the patients were classified as the combination therapy (C) group. In cases where ezetimibe was administered to those not receiving any lipid-lowering therapy (N group), the patients were classified as the mono-therapy (M) group. The concomitant use of antihypertensives, antidiabetics, and antiplatelet drugs were allowed in the study, but starting any other new drugs, discontinuing any drug, or changing dosages were not allowed during the study period.

Blood sampling and analytical methods

Fasting blood samples were obtained from the patients and measurements of all study parameters were performed in a laboratory in Tokyo Women's University Hospital. The laboratory data (assays) included total cholesterol (TC; cholesterol dehydrogenase assay), triglycerides (TG; enzymatic method), high-density lipoprotein cholesterol (HDL-C; direct method), LDL-C (direct method), and remnant-like particle-cholesterol (RLP-C; immunoadsorption). For cholesterol absorption markers, sitosterol and campesterol, which are vegetable sterols not synthesized in the body, as well as cholestanol, which is generated during bile acid synthesis, excreted in the bile, and reabsorbed, were measured. Lathosterol was measured as a cholesterol synthesis marker because it is a precursor of cholesterol that is generated by the rate-limiting step of cholesterol biosynthesis. These cholesterol absorption/synthesis markers were measured in serum by gas chromatography [13] and reported after dividing by TC because TC and cholesterol absorption/synthesis markers have a strong relationship [14]. Fasting blood glucose (FBG; hexokinase UV method), A1C (latex agglutination assay), and C-Peptide Reactivity (CPR; chemiluminescent enzyme immunoassay) were measured in order to assess glucose metabolism, while high-sensitivity C-reactive protein (hs-CRP; nephelometry) was measured as a marker of inflammation. As for A1C, the National Glycosylated Standard Program aligned value was reported.

Age, body mass index (BMI), waist circumference, blood pressure, duration of DM, complications, drugs for concomitant diseases, and risk factors for coronary heart diseases (history of coronary artery disease, stroke, and arteriosclerosis obliterans, hypertension, smoking status, and the family history of coronary artery disease) were investigated.

The cholesterol absorption and synthesis markers were compared between the S and N groups and between those with and without microvascular complications in the N group. The linear trend was examined between the clinical characteristics and the quartiles of the cholesterol absorption markers. The lipids were compared before and 12 weeks after the administration of ezetimibe.

This study was approved by the ethical committee of Tokyo Women's Medical University School of Medicine and was registered in advance with the University Hospital Medical Information Network (U-MIN; U-MIN No.: 000002070, receipt No.: R000002498).

Statistical analysis

Chi-squared tests and paired *t*-tests were used to compare proportions and means between the two groups. Analysis of variance (ANOVA) was used to compare means, and a logistic regression model was used to compare proportions across strata. A p-value < 0.05 was considered statistically significant. All statistical analyses were

performed using SPSS for Windows, version 16.0 (SPSS, Inc., Chicago, IL, USA).

Results

Table 1 shows the clinical data for the patients enrolled in the N and S groups. Patients in the S group, in comparison to those in the N group, were significantly older and more obese and had higher proportions of users of buiguanides/thiazolidinediones, insulin and antihypertensive drugs and patients with past history of coronary artery disease. Patients in the S group had significantly lower levels of the synthesis markers and higher levels of the absorption markers than those in the N group.

In the N group, LDL-C and HDL-C levels were increased, and the cholesterol synthesis markers and CPR levels were decreased with an increase of cholesterol absorption marker levels (Table 2). There was no trend in the relationship between the cholesterol absorption markers and the clinical characteristics (Table 2). However, the cholesterol absorption marker levels were significantly higher in patients with microvascular complications than in those without (30.4 ± 12.4 vs. 25.2 ± 9.1 μg/mg *10^3, p = 0.021; Figure 2), and this trend did not change after adjusting for sex, duration of DM, A1C, and systolic blood pressure at baseline (p = 0.034). Although the opposite relationship was seen between the levels of cholesterol synthesis markers and the presence/absence of microvascular complications, there was no statistical significance.

Lipid-lowering effect of ezetimibe

Table 3 shows the results of the administration of ezetimibe in the patients with hyper-LDL cholesterolemia. TC was significantly decreased by the administration of ezetimibe, and the relative decrease was -13% in all treated patients, -12.5% in patients of the M group, and -11.0% in patients of the C group, respectively. Similarly, LDL-C levels were significantly decreased, and the relative decrease was -19.7% in all treated patients, -20.7% in patients of the M group, and -15.5% in patients of the C group, respectively. The favorable changes of HDL-C, RLP-C, hs-CRP, and TG were observed both in all treated patients and in patients of the M group. The relative change in all treated patients and patients of the M group was 5.9% and 6.8% for HDL-C, -13.4% and -16.0% for RLP-C, -5.8% and -5.3% for hs-CRP, and -23.1% and -21.2% for TG (only in the patients with TG ≥ 150 mg/dL), respectively. The similar tendency was shown in the changes of the C group, but they were not statistically significant. Ezetimibe treatment significantly decreased the levels of the cholesterol absorption marker levels and increased cholesterol synthesis marker levels in all treated patients.

During the study period, there was neither a significant change in glucose and CPR levels nor adverse events that were attributable to ezetimibe.

	No treatment group	Statins-treatment group	p-value
Number	121	59	
Men (%)	73.6	57.6	0.04
Age (years)	60.9 ± 11.4	67.0 ± 9.9	<0.0001
Duration of diabetes (years)	12.7 ± 9.2	16.6 ± 8.8	0.007
Body Mass Index (kg/m^2)	25.0 ± 4.9	26.7 ± 4.0	0.029
Waist circumference (cm)	89.1 ± 10.8	93.0 ± 9.8	0.019
Systolic Blood Pressure (mmHg)	133.6 ± 12.2	135.2 ± 15.8	N.S
Diastolic Blood Pressure (mmHg)	74.9 ± 10.0	71.9 ± 12.5	N.S
Total cholesterol (mg/dL)	221.2 ± 32.9	204.8 ± 28.9	0.001
Triglycerides (mg/dL)	136.0 ± 152.9	166.3 ± 145.3	N.S
HDL cholesterol (mg/dL)	55.7 ± 14.9	54.6 ± 13.3	N.S
LDL cholesterol (mg/dL)	137.2 ± 26.6	115.9 ± 22.9	<0.001
RLP cholesterol (mg/dL)	6.7 ± 16.4	7.0 ± 9.2	N.S
Cholesterol absorption marker/total cholesterol (μg/mg*10^3)	27.4 ± 9.3	33.5 ± 18.3	<0.05
Cholesterol synthesis maker/total cholesterol (μg/mg*10^3)	9.1 ± 5.1	5.8 ± 3.5	<0.001
A1C (%)	7.4 ± 1.0	7.6 ± 1.1	N.S
Fasting blood glucose (mg/dL)	138.6 ± 43.1	139.1 ± 46.3	N.S
CPR (ng/mL)	1.7 ± 1.0	2.1 ± 1.7	N.S
Concomitant drugs (%)			
Sulfonylurea drugs	40.5	47.5	N.S
α-glucosidase inhibitors	24.0	32.2	N.S
Biguanides/Thiazolidinediones	31.4	49.2	0.023
Insulin	33.1	52.5	0.015
Antihypertensive drugs	38.0	76.3	<0.001
Antiplatelet agents	17.6	36.2	0.008
Risk factors (%)			
Smoker	19.0	15.3	N.S
Family history of coronary artery disease	3.3	5.1	N.S
History of coronary artery disease	4.2	18.6	0.004
History of stroke	7.5	5.1	N.S
History of peripheral artery disease	0.8	1.7	N.S

CPR: C-peptide reactivity. CPR (reference value): 1.2 to 2.0 ng/mL. Data are expressed as mean ± SD. HDL, high-density lipoprotein; LDL, low-density lipoprotein; RLP, remnant-like particle; A1C, hemoglobin A_{1C}.

Table 1: Clinical data of study patients.

	Quartiles of cholesterol absorption marker/total cholesterol (μg/mg*10³)				
	Q1	Q2	Q3	Q4	P-value
	(<4.6)	(4.6-5.6)	(5.6-7.2)	(≥7.3)	
Number of subjects	30	30	30	31	
Men (%)	20 (70.0)	25 (83.3)	25 (83.3)	18 (58.1)	N.S.
Age (years)	60.4 ± 10.1	61.7 ± 11.8	61.0 ± 12.1	60.6 ± 12.0	N.S.
Duration of diabetes (years)	10.9 (7.9)	12.9 (10.1)	13.5 (9.2)	12.8 (9.5)	N.S.
Body Mass Index (kg/m²)	25.2 ± 4.1	25.1 ± 5.7	25.6 ± 5.1	24.2 ± 4.7	N.S.
Waist circumference (cm)	90.7 ± 9.7	89.8 ± 10.4	89.3 ± 11.8	86.5 ± 11.1	N.S.
Systolic BP (mmHg)	135.1 ± 11.3	133.2 ± 12.5	130.3 ± 11.4	135.7 ± 13.3	N.S.
Diastolic BP (mmHg)	76.7 ± 10.5	74.3 ± 11.4	74.3 ± 9.2	74.8 ± 9.3	N.S.
Triglycerides (mg/dL)	157.1 ± 137.6	108.1 ± 64.1	170.1 ± 256.5	109.5 ± 67.7	N.S.
HDL cholesterol (mg/dL)	50.4 ± 10.4	55.7 ± 16.8	54.2 ± 13.6	62.4 ± 15.8	0.003
LDL cholesterol (mg/dL)	128.6 ± 31.3	131.5 ± 18.1	143.4 ± 27.3	145.0 ± 25.4	0.004
RLP cholesterol (mg/dL)	6.2 ± 7.0	4.5 ± 2.6	5.3 ± 2.4	5.2 ± 3.2	N.S.
Cholesterol synthesis marker/total cholesterol (μg/mg*10³)	2.4 ± 1.7	2.1 ± 1.4	2.0 ± 1.3	1.6 ± 0.9	0.014
A1C (%)	7.5 ± 1.2	7.4 ± 1.1	7.4 ± 1.0	7.2 ± 0.9	N.S.
Fasting blood glucose (mg/dL)	144.0 ± 32.4	147.7 ± 58.0	135.5 ± 44.1	127.5 ± 32.0	N.S.
CPR (ng/mL)	2.0 ± 1.0	1.8 ± 1.1	1.7 ± 1.1	1.3 ± 0.8	0.009
hs-CRP (ng/mL)	1098.2 ± 1560.4	1506.4 ± 1936.4	971.8 ± 1140.0	877.4 ± 1799.3	N.S.
History of coronary artery disease (%)	1 (3.3)	2 (6.7)	1 (3.3)	1 (3.3)	N.S.
History of stroke (%)	4 (13.3)	0 (0.0)	2 (6.7)	3 (10.0)	N.S.
Hypertension (%)	12 (40.0)	10 (33.3)	8 (26.7)	12 (38.7)	N.S.
Smoking (%)	7 (23.3)	4 (13.3)	4 (13.3)	8 (25.8)	N.S.

CPR: C-peptide reactivity. CPR (reference value): 1.2 to 2.0 ng/mL, hs-CRP: high-sensitivity C-reactive protein

Table 2: Clinical data according to quartiles of cholesterol absorption markers in 121 type-2 diabetic patients without any lipid lowering therapy.

Discussion

We have shown that the lipid-lowering treatment of statins reduced cholesterol synthesis but increased cholesterol absorption in patients with T2DM. Moreover, among the patients not receiving treatment for dyslipidemia, cholesterol absorption was significantly higher in the cases with microvascular complications than in those without the complications. The administration of a cholesterol absorption inhibitor, ezetimibe, significantly reduced LDL-C, RLP-C, and hs-CPR levels and increased HDL-C levels in patients with hyper LDL-cholesterolemia. Thus, ezetimibe may be a useful therapeutic option for dyslipidemia by additionally preventing vascular complications in patients with T2DM.

Several large-scale clinical trials have verified the usefulness of statins for inhibiting cholesterol synthesis in the liver and reducing LDL-C levels and preventing CVD [4,5]. Recently, ezetimibe, which is a cholesterol transporter inhibitor and an alternative approach for reducing LDL-C levels, has been approved. This has attracted attention as a new option for the treatment of dyslipidemia in consideration of the currently increased number of patients with dyslipidemia due to an increased dietary fat intake in Japan [1,2,15]. Accumulated data have recently highlighted cholesterol absorption as an important CVD risk factor [16-18]. A subanalysis of the 4S study has shown that CVD events were not decreased by the administration of statins in the study group of subjects with high cholesterol absorption [16]. The DEBATE study showed that CVD events were more common in patients with elevated cholesterol absorption than in those without, although LDL-C levels were the same in both groups [17]. Moreover, the Framingham Offspring Study [18] has shown that cholesterol absorption and synthesis markers were better predictors of CVD than traditional lipid risk factors. Cholesterol synthesis is reduced by the administration of statins, while cholesterol absorption shows a compensatory increase in patients on statin therapy [19,20]. These findings were concordant with our findings in T2DM.

The positive relationship between cholesterol absorption and LDL-C levels that was shown in our study has already been reported in nondiabetic patients with dyslipidemia [14,20]. The positive relationship between cholesterol absorption and HDL-C levels in our study was somewhat unexpected because cholesterol absorption seems to be a positive risk factor of CVD. The reason is not known, but a similar finding was previously reported in the prospective DEBETE Study [16]. In our study, the endogenous insulin levels (fasting CPR) decreased with increased levels of the cholesterol absorption marker, although glucose indicators and the duration of DM did not have any trend. The reason for this is not known. However, there is a possibility that the cholesterol absorption accelerates the secretion of chylomicron from small intestine, and leads to over transportation of cholesterol, TG and free fatty acids. It is reported that the excess free fatty acids promotes impairment of endogenous insulin secretion in pancreatic β-cell (= pancreatic β-cell lipotoxisity) [21]. Moreover, the levels of the cholesterol absorption marker were significantly higher in cases with microvascular complications than in those without. These findings might suggest that patients who have worse β-cell function with higher absorption marker levels were more likely to have microvascular complications, although the underlying mechanism is not known. A study from Japan showed that the coadministration of ezetimibe enhanced the proteinuria-lowering effects of pitavastatin in nondiabetic chronic kidney disease patients partly through a cholesterol-independent manner [22]. Both micro- and macro-vascular complications may share a common causal mechanism: advanced glycation end-products [23], inflammation processes, and/or oxidative stress [24]. Thus, the relationship between cholesterol absorption and microvascular diseases should be further investigated in the future. Previously, a study conducted in Finnish patients with T2DM showed that cholesterol absorption had an inverse relationship with insulin concentrations [25]. Our subjects were leaner and had a far longer duration of DM than the subjects in the Finnish study.

Our study showed that LDL-C levels were reduced by approximately 20%, and hypertriglyceridemia was significantly improved by the 12-week administration of ezetimibe. These findings are in accordance with previous reports [26,27]. Moreover, ezetimibe decreased RLP-C levels, which reflect remnants in the blood. Remnants, as well as TC, are recognized as risk factors for arteriosclerosis because they directly enter into the vascular endothelium and are taken up by macrophages without degeneration, leading to arteriosclerosis by inducing foam cell formation [28]. It has been reported that patients who are possibly insulin resistant have postprandial hyperlipidemia with prolonged triglyceride metabolism and high remnant levels [29]. In addition, it has been reported that RLP-C levels are elevated in patients with T2DM [30]. Ezetimibe suppressed chylomicron secretion from the small intestine and improved postprandial hyperlipidemia [31,32]. Thus, the improvement of postprandial hyperlipidemia by ezetimibe may relate to decreased levels of RLP-C in patients with T2DM. Kugiyama et al. reported that RLP-C was a risk factor for coronary events [33]. Thus, the decrease of RLP-C due to ezetimibe may be associated with the lowering of hs-CRP found in this study. In this study, the absorption marker levels were reduced and the synthesis marker levels were increased after the administration of ezetimibe. These results are also in accordance with a previous report [20].

		Baseline	Week 12	% change	p value
All treated patients (n = 70)					
Total cholesterol	(mg/dL)	228.8 ± 29.0	198.0 ± 26.1	-13.0 ± 10.1	<0.001
Triglycerides	(mg/dL)	136.4 ± 110.3	119.1 ± 89.4	-5.0 ± 46.2	N.S.
TG ≥ 150 mg/dL (n = 20)	(mg/dL)	249.7 ± 145.1	182.2 ± 100.6	-23.1 ± 28.9	0.005
HDL cholesterol	(mg/dL)	54.1 ± 12.3	56.9 ± 12.6	5.9 ± 11.0	<0.001
HDL cholesterol <40 mg/dL (n = 5)	(mg/dL)	32.8 ± 5.9	36.0 ± 6.0	10.5 ± 11.5	N.S.
LDL cholesterol	(mg/dL)	145.2 ± 21.3	115.6 ± 23.1	-19.7 ± 16.2	<0.001
RLP cholesterol	(mg/dL)	5.8 ± 5.4	4.4 ± 2.8	-13.4 ± 29.9	<0.001
RLP cholesterol ≥5.2 (n = 23)	(mg/dL)	10.1 ± 7.7	6.1 ± 4.1	-34.4 ± 25.7	<0.001
Cholesterol absorption marker/total cholesterol	(mg/mg*103)	7.1 ± 3.7	5.8 ± 2.1	-11.9 ± 26.4	<0.001
Cholesterol synthesis marker/total cholesterol	(mg/mg*103)	1.8 ± 1.2	3.1 ± 1.7	90.8 ± 59.4	<0.001
Fasting blood glucose	(mg/dL)	146.8 ± 49.2	147.6 ± 37.9	8.2 ± 39.0	N.S.
A1C	(%)	7.4 ± 0.8	7.5 ± 0.9	1.8 ± 6.2	N.S.
CPR	(ng/mL)	1.7 ± 1.1	1.7 ± 1.1	29.2 ± 106.6	N.S.
hs-CRP	(ng/mL)	1183.2 ± 1542.6	792.9 ± 866.6	-5.8 ± 57.0	0.003
Monotherapy (n=57)					
Total cholesterol	(mg/dL)	228.9 ±28.4	199.4 ± 25.3	-12.5 ± 9.5	<0.001
Triglycerides	(mg/dL)	135.4 ± 110.5	117.0 ± 94.0	-7.5 ± 47.8	N.S.
TG ≥ 150 mg/dL (n = 17)	(mg/dL)	241.9 ± 150.4	180.9 ± 107.3	-21.2 ± 30.8	0.02
HDL cholesterol	(mg/dL)	54.2 ± 12.6	57.6 ± 13.2	6.8 ± 10.4	<0.001
HDL cholesterol <40 mg/dL (n = 4)	(mg/dL)	32.8 ± 5.9	36.0 ± 6.0	10.5 ± 11.5	N.S.
LDL cholesterol	(mg/dL)	146.7 ± 21.2	115.5 ± 21.0	-20.7 ± 13.7	<0.001
RLP cholesterol	(mg/dL)	5.8 ± 5.4	4.3 ± 3.0	-16.0 ± 30.0	0.001
RLP cholesterol ≥5.2 (n = 20)	(mg/dL)	9.7 ± 7.7	6.0 ± 4.4	-34.5 ± 26.1	0.002
Cholesterol absorption marker/total cholesterol	(μg/mg*10^3)	6.7 ± 2.7	5.7 ± 1.8	-10.7 ± 25.1	<0.001
Cholesterol synthesis marker/total cholesterol	(μg/mg*103)	1.9 ± 1.2	3.3 ± 1.6	93.6 ± 61.7	<0.001
Fasting blood glucose	(mg/dL)	145.5 ± 47.0	149.3 ± 38.3	9.4 ± 38.8	N.S.
A1C	(%)	7.3 ± 0.8	7.4± 0.9	1.6 ± 8.6	N.S.
CPR	(ng/mL)	1.6 ± 1.1	1.7 ± 1.1	34.1 ± 110.7	N.S.
hs-CRP	(ng/mL)	1089.7 ± 1346.2	717.7 ± 705.0	-5.3 ± 56.9	0.011
Combination (Ezetimibe + Statins) therapy (n=13)					
Total cholesterol	(mg/dL)	222.0 ± 33.7	194.9 ± 29.6	-11.0 ± 16.5	0.029
Triglycerides	(mg/dL)	137.5 ± 105.6	127.8 ± 58.3	6.7 ± 33.2	N.S.
TG≥150 mg/dL (n=3)	(mg/dL)	293.7 ± 125.0	189.3 ± 62.7	-33.8 ± 12.3	N.S.
HDL cholesterol	(mg/dL)	53.7 ± 11.8	53.9 ± 9.4	2.0 ± 12.7	N.S.
HDL cholesterol <40 mg/dL (n=1)	(mg/dL)	32.8 ± 5.9	36.0 ± 6.0	10.5 ± 11.5	N.S.
LDL cholesterol	(mg/dL)	141.0 ± 20.2	114.2 ± 32.3	-15.5 ± 24.5	0.009
RLP cholesterol	(mg/dL)	5.6 ± 5.3	4.5 ± 2.0	-2.5 ± 28.1	N.S.
RLP cholesterol ≥5.2 (n=3)	(mg/dL)	12.5 ± 8.6	6.9 ± 2.1	-33.6 ± 27.4	N.S.
Cholesterol absorption marker/total cholesterol	(μg/mg*10^3)	9.1 ± 6.6	6.5 ± 3.0	-17.4 ± 32.4	<0.05
Cholesterol synthesis marker/total cholesterol	(μg/mg*10^3)	1.3 ± 1.0	2.2 ± 1.8	78.8 ± 48.4	<0.05
Fasting blood glucose	(mg/dL)	152.1 ± 60.0	140.3 ± 36.6	2.6 ± 40.9	N.S.
A1C	(%)	7.5 ± 0.8	7.6 ± 0.7	2.6 ± 5.4	N.S.
CPR	(ng/mL)	2.0 ± 1.3	1.7 ± 1.1	7.9 ± 87.1	N.S.
hs-CRP	(ng/mL)	1009.1 ± 1037.1	775.0 ± 692.8	-5.2 ± 62.1	N.S.

A1C, hemoglobin A_{1c}; CPR: C-peptide reactivity, hs-CRP: high-sensitivity C-reactive protein, HDL: high density lipoprotein, LDL: low density lipoprotein, RLP: remnant-like lipoprotein. CPR (reference value): 1.2 to 2.0 ng/mL.

Table 3: Effect of ezetimibe in 70 patients with hyper-LDL-cholesterolemia

One limitation of our study is that the number of patients was too small to show a statistically significant effect of ezetimibe in the statin combination therapy group. Alternatively, the low drug (ezetimibe) adherence in statin combination therapy group might have caused the insignificant changes on lipid profiles. Regrettably, we have not confirmed the drug adherence rate in this study. Nevertheless, the favorable change in lipids and inflammation markers was seen in the statin combination therapy group. Thus, a large-scale and replicable clinical trial needs to be done in the future in order to confirm the improvement suggested by our data.

In conclusion, ezetimibe may be a useful therapeutic option to prevent micro- and macrovascular complications for dyslipidemia in patients with T2DM.

Competing Interests

This study has not been published or submitted elsewhere, and no ethical problems or conflicts of interest are declared.

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CARDIO VASCULAR DIABETOLOGY

ORIGINAL INVESTIGATION Open Access

Relationship between hemoglobin A1c and cardiovascular disease in mild-to-moderate hypercholesterolemic Japanese individuals: subanalysis of a large-scale randomized controlled trial

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Abstract

Background: Although the ADA/EASD/IDF International Expert Committee recommends using hemoglobin A1c (HbA1c) to define diabetes, the relation between HbA1c and cardiovascular disease (CVD) has not been thoroughly investigated. We analyzed this relation using clinical data on Japanese individuals with hypercholesterolemia.

Methods: In the large-scale MEGA Study 7832 patients aged 40 to 70 years old with mild-to-moderate hypercholesterolemia without CVD were randomized to diet alone or diet plus pravastatin and followed for >5 years. In the present subanalysis of that study a total of 4002 patients with baseline and follow-up HbA1c data were stratified according to having an average HbA1c during the first year of follow-up <6.0%, 6.0%-<6.5%, or ≥6.5% and their subsequent 5-year incidence rates of CVD compared according to sex, low-density lipoprotein cholesterol (LDL-C), and treatment arm.

Results: Overall, risk of CVD was significantly 2.4 times higher in individuals with HbA1c ≥6.5% versus <6.0%. A similar relation was noted in men and women (hazard ratio [HR], 2.1; p <0.01 and HR, 3.0; p <0.01, respectively) and was regardless of treatment arm (diet alone group: HR, 2.2; p <0.001; diet plus pravastatin group: HR, 1.8; p = 0.02). Spline curves showed a continuous risk increase according to HbA1c level in all subpopulations studied.

Conclusions: In hypercholesterolemic individuals the risk of CVD increases linearly with HbA1c level. This significant contribution by elevated HbA1c to increased CVD is independent of pravastatin therapy, and thus requires appropriate HbA1c management in addition to lipids reduction.

Keywords: Hemoglobin A1c (HbA1c), cardiovascular disease (CVD), hypercholesterolemia, HMG CoA reductase inhibitor, pravastatin, MEGA Study

Background

Clinical markers such as fasting plasma glucose (FPG), oral glucose tolerance test, and postprandial glucose are commonly used to define diabetes or impaired glucose tolerance [1-3]. However, in 2009 an International Expert Committee assembled by the American Diabetes Association (ADA), European Association for the Study of Diabetes (EASD), and International Diabetes Federation (IDF) announced that HbA1c assay is a more reliable marker to diagnose diabetes, using a cutpoint of ≥6.5% [4]. Observational studies indicate that measuring HbA1c, compared with a single measure of glucose concentration, better captures the impact of long-term glycemic exposure and severity of diabetic complications. Epidemiologic data have also demonstrated relations between HbA1c and microvascular and macrovascular disease [5-7]. On the other hand, data are scarce for

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patients with a specific disease background such as hypercholesterolemia.

This subanalysis evaluated the relation between HbA1c and CVD using data from the long-term, large-scale Management of Elevated Cholesterol in the Primary Prevention Group of Adult (MEGA) Study conducted in Japan in the late 1990s to mid-2000s [8,9].

Methods

The design, baseline characteristics, and major outcomes of the prospective, randomized, open-label, blinded endpoints MEGA Study have been described previously [8,9]. Briefly, 7832 patients (2476 men and 5356 postmenopausal women) aged 40-70 years with mild-to-moderate hypercholesterolemia (total cholesterol [TC] level, 5.7-6.0 mmol/L) without CVD were randomly allocated to either the diet group or diet plus pravastatin (10-20 mg/day, the approved dose in Japan) group for a mean follow-up period of 5.3 years. Patients in both arms were counseled to follow the National Cholesterol Education Program (NCEP) Step I diet [10] throughout the study period. Pravastatin was initiated at 10 mg/day; however, if the TC level did not decrease to ≤5.7 mmol/L the dosage could be uptitrated to 20 mg/day, in compliance with Japanese dosing instructions. Patients whose TC remained >5.7 mmol/L, even after enhancement of assigned treatment, could be switched to other aggressive treatments including other statins. Concomitant treatment for complications was not restricted in both groups. The primary composite endpoint was first occurrence of coronary heart disease (CHD) comprising fatal and nonfatal myocardial infarction, angina pectoris, cardiac/sudden death, and coronary revascularization procedure. Secondary endpoints included all strokes, CHD plus ischemic stroke, all CVD events, and total mortality.

Patients were evaluated by their attending physician at 1, 3, and 6 months and every 6 months thereafter. Health checkups at each clinic visit included biochemical tests, including HbA1c levels, and assessment of patient adherence to treatment. For each event, detailed information was obtained from physicians and evaluated by the blinded Endpoints Committee according to established criteria. TC, high-density lipoprotein cholesterol (HDL-C), triacylglycerides (TG), and lipoprotein(a) (Lp [a]) levels were centrally measured at the same laboratory using methods standardized by the Centers for Disease Control and Prevention (Atlanta, GA). Low-density lipoprotein cholesterol (LDL-C) level was estimated by Friedewald's formula. Fasting glucose, HbA1c, and other laboratory values were measured at each participating institution. Because the Japan Diabetes Society (JDS) method was used to measure HbA1c, which has values that are 0.3%-0.4% percent lower than National Glycohemoglobin Standardization Program (NGSP) values [11], for this report we converted all HbA1c values to NGSP values by the following formula: HbA1c (%) = 0.0981 × International Federation of Clinical Chemistry (IFCC) value (mmol/L) [10.39 × JDS value (%) - 16.8] + 1.95 [12].

We analyzed data on patients whose HbA1c value was determined during the first 12 months of the study (5 values per patient; baseline, and at 1, 3, 6 and 12 months). Using these data, we assessed relations between average HbA1c value for the first 12 months and occurrence of CVD events including myocardial infarction, angina, cardiac and sudden death, a coronary revascularization procedure, stroke, transient ischemic attack, and arteriosclerosis obliterans occurring during the 5 years of follow-up. Event rates were compared for three categories of HbA1c levels such as <6.0%, 6.0%-<6.5%, and ≥6.5% using the new criteria from the International Expert Committee [4]. Hazard ratios (HRs) and 95% confidence intervals (95%CIs) were estimated by multivariate Cox proportional hazards model. Relations between HbA1c and risk of CVD events were evaluated by multivariable Cox proportional hazards model with restricted quadratic spline [13]. The three knots for quartiles were adopted as optimal analysis model for this study, based on the results of comparison of a model using two and four knots for HbA1c tertiles and quintiles and that using three knots for 5.0%, 6.0%, and 7.0% of HbA1c. The multivariate models were simultaneously adjusted by sex, age, treatment arm, baseline LDL-C, baseline HDL-C, hypertension, chronic kidney disease (estimated glomerular filtration rate <60), and smoking status.

Results

Baseline clinical and demographics characteristics of the 4002 patients included in this analysis are summarized in Table 1. Two thirds of the patients (66%) were women; men were about 4 years younger than women and had a slightly higher BMI. Confirmed diabetes, and consequently average FPG and HbA1c, were higher in men, whereas confirmed hypertension was higher in women. LDL-C and HDL-C were somewhat lower, and TG higher, in men than women.

The incidence of cardiovascular events in men and women was compared among the three categories of HbA1c levels as shown in Table 2. Comparing the ≥6.5% versus <6.0% HbA1c group overall, CHD was significantly higher (HR, 3.1; p <0.01), and also in men (HR, 2.3; p <0.01) and women (HR, 4.9; p <0.01). Moreover, CVD was significantly increased (HR, 2.4; p <0.01), and in men (HR, 2.1; p <0.01) and women (HR, 2.9; p <0.01). As the HbA1c level increased, the incidence of CHD and CVD increased. Whereas, stroke incidence