Table 1. Cont.

Source	Country, region/cohort	Follow-up, yr	N (women, %)	Age, yr	Diabetes, %	Coronary heart disease, %	Outcome, n
							Ischemic stroke 294
							Hemorrhagic stroke 70
							Subarachnoid hemorrhage 121
							Peripheral arterial disease 82
Nilsson, 2012 [10]	Sweden, Västerbotten Intervention Program	Median 10	77319 (51)	Median 49	3	NR	All-cause death 2383
							CVD death 681

NR: not reported, CVD: cardiovascular disease, LCHP: low-carbohydrate/high-protein,
*not included in meta-analysis, NHS: Nurses' Health Study, HPFS: Health Professionals Follow-up Study, EPIC: European Prospective Investigation into Cancer and Nutrition.
doi:10.1371/journal.pone.0055030.t001

and incidence were not statistically significant: RR 1.10 (0.98–1.24); p = 0.12; I^2 = 0% (p = 0.41), RR 0.98 (0.78–1.24); p = 0.87; I^2 = 53% (p = 0.09), respectively. The RR in CVD mortality using the LC/HP score was not statistically significant, either: RR 1.53 (0.88-2.67); p = 0.13; I^2 = 61% (p = 0.05). There was only one study on CVD incidence using the LC/HP score, which showed a significantly elevated risk. [9] There was a positive dose-response in 2 analyses. [7,9].

Discussion

Our systematic review and meta-analyses of worldwide reports suggested that low-carbohydrate diets were associated with a significantly higher risk of all-cause mortality in the long run. They also suggested that low-carbohydrate diets might not be protective or harmful in terms of CVD mortality and incidence. These findings support the hypothesis that the short-term benefits of low-carbohydrate diets for weight loss are potentially irrelevant. [13] In light of the fact that the number of people with obesity is exponentially increasing worldwide and obesity is one of the leading risk factors of mortality, [15] our findings have substantial clinical and public implications on a global scale and point to the need for the further investigation of the long-term health effects of low-carbohydrate diets and other nutritional factors.

The strength of our present study is that the analysis was mainly based on long-term large population-based data originating from multiple nations and was performed with a high level of precision and this is the first meta-analysis, to our best knowledge, on the health effects of low-carbohydrate diets. The included data were good in quality and apparently had power enough to detect the differences in the risk of these outcomes. The outcome ascertainment tools were valid, and each result was adjusted for multiple confounders and the significantly increased pooled RRs for all-cause mortality were robust in that the RRs based on both of the methods were almost identical and statistically significant. Heterogeneity of the results of the component studies was modest: low heterogeneity suggests that the each result was consistent and most variation was attributable to chance alone, and the large I^2 values in some analyses indicated that the range of the plausible risk estimates was wide, generally because of the diversity of study design, population backgrounds and ethnicities. The subgroup analysis suggested that the possible major source of heterogeneity was the region or the nutrition assessment method in addition to the publication bias. The main dietary source of protein and the obesity prevalence differ across countries [33]. The length of follow-up and the gender were possibly other sources of heterogeneity but these hypotheses cannot be statistically tested in light of the scarcity of data.

Evidence has been accumulating to suggest that low-carbohydrate diets and their combination with high-protein diets are effective in weight loss [1–3] and may have favorable short-term effects on the risk markers of CVD. [4–6] Low-carbohydrate diets may be nutritionally safe and valid insofar as the carbohydrates are simple and refined, and the main source of the protein is plants. Despite these facts, our study did not find a cardiovascular benefit and supports their potential long-term health harm when such nutritional quality is not considered. Low-carbohydrate diets tend to result in reduced intake of fiber and fruits, and increased intake of protein from animal sources, cholesterol and saturated fat, [27,30,34] all of which are risk factors for mortality and CVD. [13,14] It is postulated that differences in dietary bioactive components such as specific free fatty acids, protein, fiber, minerals, vitamins and phytochemicals are involved. [7] Subgroup analyses suggested that low-carbohydrate diets might increase the

Table 2. Methodological assessments of the included studies.

Source	Parameter	Outcome measures	Referent	Comparator	Adjustment factors
Garcia-Palmieri, 1980* [23]	Carbohydrate intake	Coefficient			Alcohol, systolic blood pressure, cholesterol, cigarettes smoked, and blood glucose
McGee, 1984* [24]	Carbohydrate intake	Coefficient			Energy intake, blood pressure, serum cholesterol, cigarettes smoked per day, body weight (in pounds), and physical activity index
McCullough, 2000* [25]	Healthy eating index-f	Relative risk	Quintile 5	Quintile 1	Age (5-y categories), smoking (never, past, 1–14 cigarettes/d, 15–24 cigarettes/d, or ≥25 cigarettes/d), time period, body mass index (quintiles), alcohol intake (7 categories), physical activity (6 categories of metabolic equivalents), history of hypertension or hypercholesterolemia at baseline, total energy intake (quintiles), postmenopausal status, postmenopausal hormone use, multivitamin and vitamin E supplement use
McCullough, 2000* [26]	Healthy eating index-f	Relative risk	Quintile 5	Quintile 1	Age (5-y categories), body mass index (quintiles), smoking (never, past, 1–14 cigarettes/d, 15–24 cigarettes/d, ≥25 cigarettes/d), alcohol intake (7 categories), physical activity (6 categories), total energy intake (quintiles), time period, multivitamin use, vitamin E use, and diagnosis of hypercholesterolemia and hypertension at baseline
McCullough, 2002* [14]	Recommended Food Score	Relative risk	Quintile 5	Quintile 1	Age (5-y categories), smoking (never, past, 1–14 cigarettes/d, 15–24 cigarettes/d, >25 cigarettes/d), time period, body mass index (quintiles), physical activity (6 categories of metabolic equivalents), total energy intake (quintiles), history of hypertension or hypercholesterolemia at baseline, vitamin E and multivitamin supplement, and for women, postmenopausal hormone use
Fung, 2001* [27]	Prudent pattern/ Western pattern	Relative risk	Quintiles 4,5/1	Quintiles 1/4,5	Age, period, smoking, body mass index, hormone replacement therapy, aspirin use, caloric intake, family history, history of hypertension, multivitamin and vitamin E use, and physical activity
Diehr, 2003* [28]	Diet quality	Years of life in 10 yr, CVD incidence	Healthy diet	Unhealthy diet (high fat, low fiber, low carbohydrate, high protein, high calorie)	Demographics, health, behaviors, and baseline health variables
Oh, 2005 [29]	Carbohydrate intake	Relative risk	Quintile 5	Quintile 1	Age (5-year categories), body mass index (five categories), smoking (never, past, current 1–14, 15–24, ≥25 cigarettes/day), alcohol intake (four categories), parental history of myocardial infarction, history of hypertension, hypercholesterolemia, and diabetes, menopausal status and postmenopausal hormone use, aspirin use (five categories), multivitamin use, vitamin E supplement use, physical activity (hours/week, five categories), energy, cereal fiber (quintiles), saturated fat, monounsaturated fat, polyunsaturated fat, trans-fat, and omega-3 fatty acids (quintiles)
Halton, 2006 [30]	Low carbohydrate score	Relative risk	Decile 1	Decile 10	Age (in 5-year categories), body-mass index (<22.0, 22.0 to 22.9, 23.0 to 23.9, 24.0 to 24.9, 25.0 to 27.9, 28.0 to 29.9, 30.0 to 31.9, 32.0 to 33.9, 34.0 to 39.9, or ≥40.0), smoking status (never, past, or current [1 to 14, 15 to 24, or ≥25 cigarettes a day]), postmenopausal hormone use (never, current use, or past use), hours of physical activity per week (<1, 1 to 2, 2 to 4, 4 to 7, or >7), alcohol intake (0, <5 g per day, 5 to 14 g per day, or ≥15 g per day), number of times aspirin was used per week (<1, 1 to 2, 3 to 6,7 to 14, or ≥15), use of multivitamins (yes or no), use of vitamin E supplement (yes or no), history of hypertension (yes or no), history of hypercholesterolemia (yes or no), parental history of myocardial infarction (yes or no), and total calories
Beulens, 2007 [31]	Carbohydrate intake	HR	Quartile 4	Quartile 1	Age, hypertension, cholesterolemia, smoking (never/past/current smoking of 1 to 10, 11 to 20, and ≥20 cigarettes), body mass index, mean systolic blood pressure, total physical activity, menopausal status (pre or post), hormone replacement therapy use, oral contraceptives use, alcohol intake (≤10, 11 to 25, 26 to 50, ≥50 g/day energy-adjusted), total energy intake (in quintiles) and energy-adjusted intake of vitamin E, protein, dietary fiber, folate, saturated fat, and poly- and monounsaturated fat
Lagiou, 2007 [11]	Low carbohydrate score	HR	Per decreasing tenth of carbohydrate intake		Height (cm, continuously), body mass index (<25, 25–29.99 and 30 kg m2, categorically), smoking status (never smokers, former smokers of <10 cigarettes, former smokers of 10–14 cigarettes, former smokers of 15–19 cigarettes, former smokers of 20 or more cigarettes, current smokers of <10 cigarettes, current smokers of 10–14 cigarettes, current smokers of 15–19 cigarettes, current smokers of 20 or more cigarettes, categorically), physical activity (from 1 (low) to 5 (high), categorically), education (0–10, 11–13 and 14 or more years in school, categorically), energy intake (per 1000 kJ day), continuously), saturated lipid intake (per 10 g, continuously) and alcohol intake (<5, 5–25 or >25 g day, categorically).

Table 2. Cont.

Source	Parameter	Outcome measures	Referent	Comparator	Adjustment factors
	LCHP score	HR	Per increasing 2 points		
Massimino, 2007* [32]	Carbohydrate intake	HR	Tertile 3	Tertile 1	Gender (male/female), age (in years), generation (second versus first), physical activity (other versus heavy/very heavy), arterial pressure (systolic and diastolic, in mmHg), degree of glucose tolerance ("dummy": normal glucose tolerance, altered fasting blood glucose, impaired glucose tolerance, and diabetes mellitus), presence of dyslipidemia (yes/no), and smoking (smoker/non-smoker)
Trichopoulou, 2007 [12]	Carbohydrate intake	HR	Per decreasing tenth of carbohydrate intake		Energy intake, gender (men, women; categorically), age (<45 years, 45–54 years, 55–64 years, ≥65 years; categorically), years of schooling (<6, 6–11, 12, ≥13; categorically), smoking (never, former and 1–10 cigs per day, 11–20 cigs per day, 21–30 cigs per day, 31–40 cigs per day, ≥41 cigs per day; ordered), body mass index (per quintile; ordered), physical activity (per quintile; ordered), and ethanol intake (<10 g per day, 10–30 g per day, ≥30 g per day; categorically).
	LCHP score	HR	Per increasing 2 points for CVD death		
			Lowest group (2–6 points) for all-cause death	Highest group (16–20 points)	
Fung, 2010 [7]	Low carbohydrate score	HR	Decile 1	Decile 10	Age, physical activity, body mass index, energy intake, alcohol intake, menopausal status and postmenopausal hormone use (women only), history of hypertension, smoking status, and multivitamin use.
Sjögren, 2010 [8]	LCHP score	HR	Lowest group (2–6 points)	Highest group (16–20 points)	Energy intake, smoking, social class, type 2 diabetes, the metabolic syndrome, lipid-lowering treatment, blood pressure–lowering treatment, waist circumference, diastolic blood pressure, insulin, C-reactive protein
Lagiou, 2012 [9]	Low carbohydrate score	HR	Per decreasing tenth of carbohydrate intake		Height (cm, continuously), body mass index (<25, 25–29.99, and ≥30, categorically), smoking status (never smokers, former smokers of <10 cigarettes, former smokers of 10–14 cigarettes, former smokers of 15–19 cigarettes, former smokers of ≥20 cigarettes, current smokers of <10 cigarettes, current smokers of 10–14 cigarettes, current smokers of 15–19 cigarettes, and current smokers of ≥20 cigarettes, categorically), physical activity (from 1 (low) to 5 (high), categorically), education (≤10, 11–13, and ≥14 years in school, categorically), diagnosis of hypertension (ever versus never), energy intake (per 1000 kJ/day, continuously), unsaturated lipid intake (per 10 g/day, continuously), saturated lipid intake (per 10 g/day, continuously), and alcohol intake (<5 g/day, 5–25 g/day, and >25 g/day, categorically)
	LCHP score	HR	Per increasing 2 points		
Nilsson, 2012 [10]	Carbohydrate intake	HR	Per decreasing tenth of carbohydrate intake		Age, body mass index, sedentary lifestyle, education, current smoking, intake of energy, alcohol, and saturated fat
	LCHP score	HR	Lowest group (2–8 points)	Highest group (14–20 points)	

CVD: cardiovascular disease, LCHP: low-carbohydrate/high-protein, HR: hazard ratio,
*not included in meta-analysis.
doi:10.1371/journal.pone.0055030.t002

risk of mortality and CVD in animal-based dietary patterns whereas they might decrease the risk in plant-based diets. [7,9,30] In our analysis, the increment in the all-cause mortality might have been partly attributable to the increased risks for CVD mortality and morbidity although they were not significant. It is possible that the beneficial effect of plant protein may have been offset by the adverse effect of animal protein in our calculations. Low-carbohydrate diets may be linked to an array of other chronic health problems. A positive cancer risk has been reportedly related to the intake of animal protein, [7] and red and processed meat consumption, [35] although the risk of cancer was found to be non-significant in our analysis. [11,12] Little is known about the

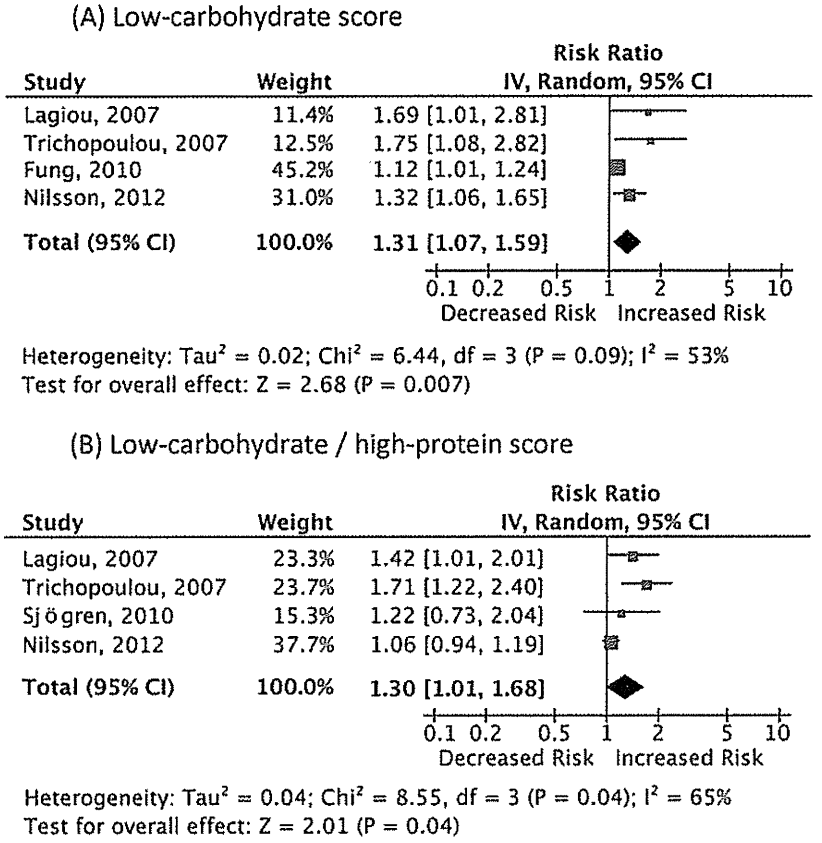

Figure 2. Adjusted risk ratios for all-cause mortality associated with low-carbohydrate diets. Analysis was done based on (A) the low-carbohydrate score and (B) the low-carbohydrate/high-protein score. Boxes, estimated risk ratios (RRs); bars, 95% confidence intervals (CIs). Diamonds, random-effects model RRs; width of diamonds; pooled CIs. The size of each box is proportional to the weight of each study in the meta-analysis. IV, inverse-variance.
doi:10.1371/journal.pone.0055030.g002

consequences of low-carbohydrate diets with respect to kidney disease, osteoporosis, and mental condition. The biology that underlies the positive correlation between low-carbohydrate diets and all-cause death is not fully explained. Further studies to clarify the mechanism are eagerly awaited.

Given the facts that low-carbohydrate diets are likely unsafe and that caloric restriction has been demonstrated to be effective in weight loss regardless of nutritional composition, [36] it would be prudent not to recommend low-carbohydrate diets for the time being. Further detailed studies to evaluate the effect of protein source are urgently needed.

Limitations

Although the quality of the included studies might not be an issue, our analysis should be interpreted in the context of the following limitations. The observational studies were scarce and moderately heterogeneous, and thus a publication bias and a residual confounding bias may have existed although we cannot assess these hypotheses. In the analysis of CVD mortality risk, there may not have been enough statistical power and the representativeness of the cohort may be poor since the data of healthcare professionals [7] dominated (**Fig. 3A**). Next, the relation may not necessarily be causal, particularly in the observational studies [37] because of possible confounding factors and biases that may not have been fully adjusted for, which may have rendered the results less valid. In our analysis, the adjustment in each component study was adequate and fair. Confounding by treatment indication [38] might bias the effect of diets. However, most of the target populations were free of chronic disease at baseline and it is less likely that the dietary habits had been modulated according to their previous health status. A dose-response of relative risk was confirmed in few studies, which might make the results less plausible. Dietary patterns may vary over the course of follow-up but updating dietary information was not done in many studies and thus the magnitude of risk may have been diluted as suggested by our subgroup analysis of the flow-up periods and the supplementary analysis by Lagiou, et al. [9] Furthermore, it is difficult to distinguish the effects of individual nutritional component. For all these limitations, however, observational studies provide good available evidence regarding potential benefit and harm, and the overall pooled estimates were robust, the temporal sequence of the events was appropriate, and the results among the included studies seemed consistent. Moreover, evidence has been accumulating to support these potential adverse outcomes. [39] With regards to external validity, it is also important to realize that the participants of the studies may not represent general populations most likely because the majority of the studies were done in Western countries and healthcare professionals dominated. It remains unclear if these diets exert a similar influence on the clinical outcome in diabetic patients.

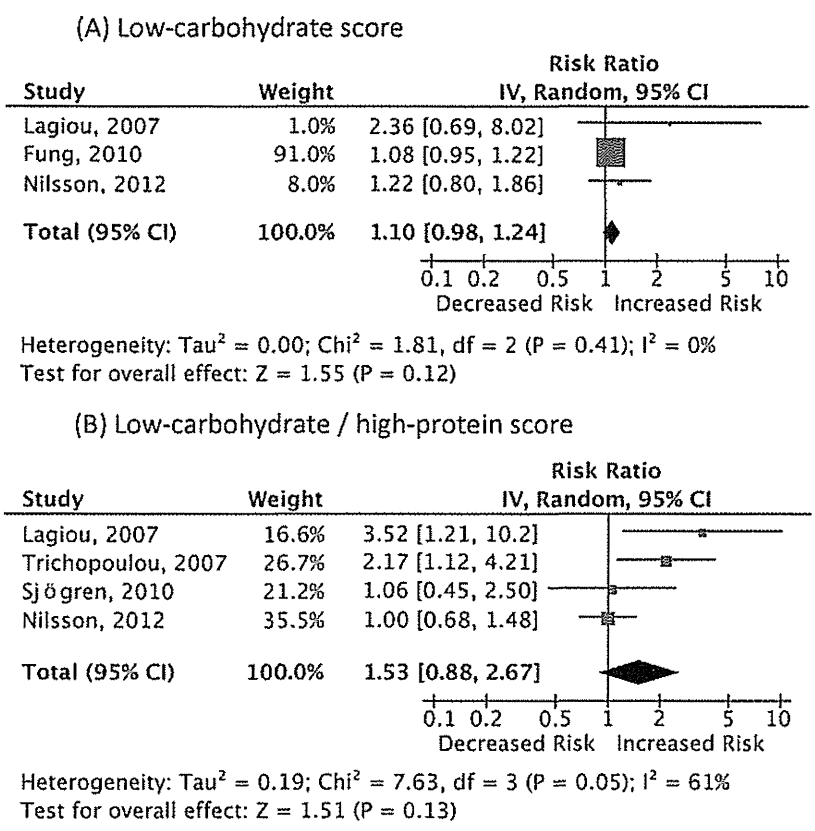

Figure 3. Adjusted risk ratios for CVD mortality associated with low-carbohydrate diets. Analysis was done based on (A) the low-carbohydrate score and (B) the low-carbohydrate/high-protein score. Boxes, estimated risk ratios (RRs); bars, 95% confidence intervals (CIs). Diamonds, random-effects model RRs; width of diamonds; pooled CIs. The size of each box is proportional to the weight of each study in the meta-analysis. IV, inverse-variance.
doi:10.1371/journal.pone.0055030.g003

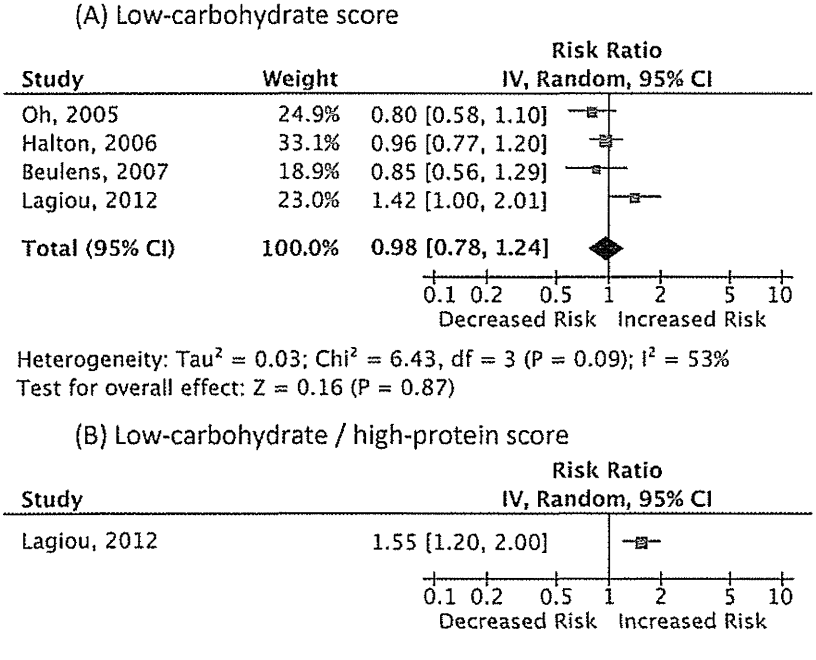

Figure 4. Adjusted risk ratios for CVD incidence associated with low-carbohydrate diets. Analysis was done based on (A) the low-carbohydrate score and (B) the low-carbohydrate/high-protein score. Boxes, estimated risk ratios (RRs); bars, 95% confidence intervals (CIs). Diamonds, random-effects model RRs; width of diamonds; pooled CIs. The size of each box is proportional to the weight of each study in the meta-analysis. IV, inverse-variance.
doi:10.1371/journal.pone.0055030.g004

Even with these limitations, none of the included studies showed a significantly reduced risk and our analysis does not favor long-term benefits of low-carbohydrate diets, which should provide physicians with an incentive to pay attention to the considerable potential adverse effects on health if such diets are implemented without considering the nature of the carbohydrates and the source of protein. [9].

Conclusions

Our meta-analysis supported long-term harm and no cardiovascular protection with low-carbohydrate diets. However, the observational studies were limited and moderately heterogeneous. Our findings underscore the imminent need for large-scale trials on the complex interactions between low-carbohydrate diets and long-term outcomes.

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Supporting Information

Table S1 Newcastle-Ottawa quality assessments of the included studies.
(DOCX)

Acknowledgments

Disclaimer: All the authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Author Contributions

Conceived and designed the experiments: HN MN. Performed the experiments: HN AG TT. Analyzed the data: HN AG TT. Contributed reagents/materials/analysis tools: HN AG TT. Wrote the paper: HN.

49:210

第53回日本老年医学会学術集会記録
〈若手企画シンポジウム2：サルコペニア―研究の現状と未来への展望―〉

6. Sarcopenic Obesity―代謝からみたサルコペニアの意義―

荒木　厚　周　赫英　森　聖二郎

Key words：高齢者，サルコペニア，糖尿病，インスリン抵抗性，炎症

（日老医誌　2012；49：210-213）

はじめに

サルコペニアは①筋肉量の減少，および②筋力または筋のパフォーマンスの低下と定義されてきている．一方，sarcopenic obesity はサルコペニアと肥満の両者が合併したものである．未だサルコペニアの定義と肥満の定義が研究によって異なるために，機能的予後，動脈硬化性疾患を予測できるかについては，未だ意見の一致を見ていない．本稿では sarcopenic obesity について概説するとともに，高齢糖尿病患者を対象に，DXA（Dual energy X-ray absorpiometry）法の筋肉量と体脂肪量より定義した sarcopenic とインスリン抵抗性，身体機能，および転倒との関連について報告する．また，sarcopenic obesity とサルコペニアとの相違点についても考察してみたい．

Sarcopenic obesity の頻度

DXA 法により，四肢の筋肉量（appendicular skeletal mass）を身長の2乗で割った Relative Skeletal Muscle Index（RSMI）を用いてサルコペニアを評価した場合，高齢者の sarcopenic obesity の頻度は5～10% であり，80歳以上になると10% を越える[1)~3)]．New Mexico Aging Study は831名の60歳以上住民を対象に，サルコペニアを若い人の RSMI の平均－2 SD 以下と定義（男性で7.26 kg/m²未満，女性で5.45 kg/m²未満）し，肥満を体脂肪率のメディアン以上と定義すると，その頻度は男性で4.4%，女性で3.0% であった[1)]．NHANES III 研究では2,982名（平均年齢77歳）を対象にサルコペニア：RSMI の5分位の下2分位（男性で9.12 kg/m²未満，女性で6.53 kg/m²未満），肥満を体脂肪率の5分位の上2分位と定義するとその頻度は男性で9.6%，女性で7.4% であった[2)]．

われわれは，2008年～2010年に入院し，DXA 法で全身骨密度検査の検査を受けた入院糖尿病患者93名（年齢：74.9±8.3歳，男35名，女性58名，BMI：23.5±4.0，罹病年数：16.5±11.3年，HbA1c：8.2±1.6%，治療法：食事のみ11名，経口薬55名，インスリン27例）を対象として sarcopenic obesity の頻度を算出した．サルコペニアは RSMI＝appendicular lean mass ÷（height)² の median 未満または5分位の下2分位と定義し，肥満は体脂肪率，BMI，または内臓脂肪面積で定義した．サルコペニアを RSMI の median 未満と定義した際のカットオフ値は男性で6.53 kg/m²未満，女性で5.72 kg/m²であった．体脂肪率の5分位の上2分位を肥満と定義すると肥満の頻度は39.6% であった．BMI 24以上を肥満と定義すると肥満の頻度は42% であった．内臓脂肪面積100 cm²以上と定義すると，内臓脂肪肥満の頻度は34.4% であった．こうした3種類の肥満の定義とサルコペニアを組み合わせて sarcopenic obesity を定義するとその頻度はそれぞれ16.7%，12.5%，14.6% であり，体脂肪率と DXA 法の RSMI median 以下を組み合わせて使った場合の頻度が最も多かった．しかし，sarcopenic obesity の肥満の定義を体脂肪，BMI，内臓脂肪量のいずれを用いるべきかについての報告はない．

サルコペニアの定義も筋量のみで定義するよりは「筋量低下かつ筋力低下また身体能力の低下」と変わりつつある[4)]．これは脂肪の筋肉へ浸潤の影響を考慮して，筋量が正確に測定できていない場合があることや筋肉の量よりも筋肉の機能の方が機能的予後を反映しやすいということに基づいている．

Sarcopenic obesity の成因・機序

Sarcopenic obesity を構成するサルコペニアと肥満の

Relationship between sarcopenic obesity or sarcopenia and insulin resistance or functional disability

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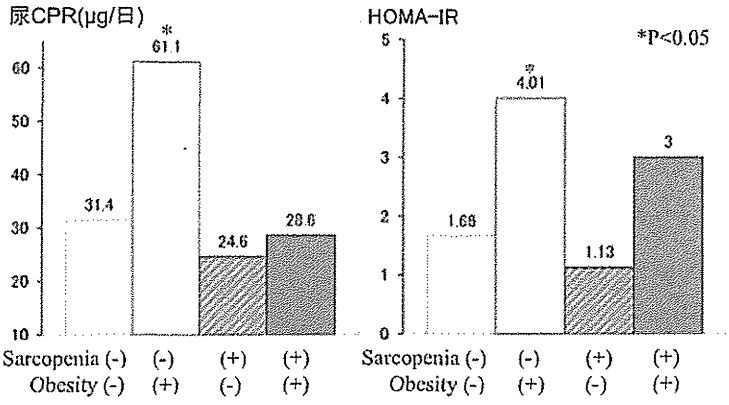

図1　Sarcopenic obesity とインスリン分泌，およびインスリン抵抗性

両者は炎症，インスリン抵抗性，低栄養，活動性低下といった共通の成因があり，これらが互いに影響し合い，悪循環を形成する．肥満による活動性低下はサルコペニアをきたし，さらに肥満をもたらす．

炎症は，肥満とサルコペニアの両者の成因に大きく関与する．65歳以上の871名を対象としたCHIANTY研究では，肥満と握力低下で定義したsarcopenic obesityの患者の血清CRP，IL-6，可溶性IL-6受容体が高値であると報告した[5]．脂肪細胞にマクロファージが浸潤するとIL-6やTNF-αなどの炎症性サイトカインが産生され，これらが筋肉に作用し，筋量や筋力の減少をもたらすことが考えられる．炎症サイトカインは脂肪量と正の相関，筋肉量と負の相関を示すという報告もある[6]．

上記の我々の患者でもRSMIと血清IL-6は負の相関を示した（$r=-0.622$，$P<0.05$）．この結果はIL-6高値が高齢者の筋力や移動能力の低下を予測するという報告と一致する[7]．機序としては，IL-6による筋肉でのIGF-1の同化作用の阻害，IL-6によるインスリン抵抗性亢進などが考えられる[8]．

インスリン抵抗性もsarcopenic obesityの重要な特徴の一つである．肥満や2型糖尿病患者で筋肉内に脂肪が蓄積するとインスリン抵抗性が惹起される．さらに，この筋肉でのインスリン抵抗性は筋力低下をもたらすことが考えられる．実際，高齢女性において握力の低下はインスリン抵抗性と関連したという報告がある[9]．高齢2型糖尿病患者では糖尿病がない人と比べて，下肢の筋力低下がおこりやすいが[10]，この糖尿病患者の下肢筋力低下もインスリン抵抗性の指標のHOMA-IRと関連した[11]．逆に，高齢糖尿病でもレジスタンス運動を行うと，除脂肪量が増加し，インスリン抵抗性が改善し，ADLが向上する[12]．

図1に示すように，上記の我々の患者でインスリン抵抗性の指標としてHOMA-IRを見ると，HOMA-IRは単なる肥満のみの患者で高値を示し，サルコペニアのみの患者では低値となり，sarcopenic obesityの患者で高値を示した（図1）．尿Cペプチドは単なる肥満のみで高値を示したことより，sarcopenic obesityではインスリン分泌がやや低下傾向があるのにインスリン抵抗性があるという状態であると考えられる．しかしながら，このsarcopenic obesityによるインスリン抵抗性は，高血糖とは関連を認めず，血糖コントロールには影響を及ぼしているとは考えにくい．

Sarcopenic obesityの予後

サルコペニアと肥満は身体機能低下の危険因子であるので，両者が重なったSarcopenic obesityは身体機能のADL低下，歩行障害，転倒などの悪影響を及ぼす．New Mexico Aging Process Studyの8年間の追跡調査では，sarcopenic obesityは対照と比較して年齢，性，活動度，高血圧，関節炎を調整しても，2.63倍IADLの低下をきたした[13]．また，New Mexico Elder Health Surveyでは，sarcopenic obesityの患者は対照と比べて要介護状態は男性で8.7倍，女性で12.0倍，歩行障害は男性で4.4倍，女性は5.5倍，転倒は男性は3.3倍，女性は2.1倍おこしやすく，そのリスクは単なる肥満やサルコペニアよりも高かった[1]．EPIDOS研究では，sarcopenic obesityは階段の昇降が対照と比べて約2倍障害されており，単なるサルコペニアでは身体機能の障害はなかった[3]．しかし，サルコペニアを筋肉量で定義した2つの断面調査では，sarcopenic obesityと身体機能との関連はなかったという報告もある[6]．

上記のわれわれの患者をサルコペニアと肥満の有無で4群に分けて比較検討した．表1に示すようにサルコペニアのみ群とsarcopenic obesity群では高齢でRSMIや

表1　研究の対象

	Obesity（−）Sarcopenia（−）(n=26)	Obesity（+）Sarcopenia（−）(n=22)	Obesity（−）Sarcopenia（+）(n=32)	Obesity（+）Sarcopenia（+）(n=16)
年齢（歳）	73.6±7.9	70.7±8.0	77.6±8.1***	78.3±6.3***
女性（%）	57.7	68.2	62.5	62.5
罹病年数	20±12	11±9*	20±11	10±6*
BMI	22.6±1.8	28.9±2.7***	20.1±2.3***	24.4±2.0*
体脂肪（%）	19.7±5.4	38.0±6.4*	20.4±8.1	34.0±4.8*
RSMI	6.7±0.7	6.8±0.8	5.3±0.5*	5.5±0.6*
大腿骨頸部 BMD	0.75±0.16	0.80±0.12	0.66±0.14*	0.69±0.13
HbA1c（%）	8.2±1.7	8.6±1.9	8.1±1.6	7.8±1.5

*P<0.05，**P<0.01，***P<0.001 vs Obesity（−），Sarcopenia（−）群

表2　サルコペニアと sarcopenic obesity の相違点

	RSMI (Sarcopenia)	Lean mass/Fat mass (Sarcopenic obesity)
年齢	r=−0.418***	n.s.
骨密度（大腿骨頸部）	r=0.526***	n.s.
血清アルブミン	r=0.218*	n.s.
Hb	r=0.268*	r=−0.240*
尿 CPR	r=0.377***	r=−0.342**
HOMA-IR	n.s.	r=−0.459**
SBP	r=−0.243*	n.s.
DBP	n.s.	r=−0.354*
MMSE	r=0.230（p=0.06）	r=−0.238（p=0.05）

*P<0.05，**P<0.01，***P<0.001，r：Spearman の相関係数

骨密度も低い傾向が見られた．肥満群，sarcopenic obesity 群とも罹病年数も短く，BMI，体脂肪量が大きかった．しかし，排泄と入浴の障害はサルコペニアのみ群と sarcopenic obesity群とで同様であり（それぞれ 38.1% vs 35.7，38.1% vs 42.9%）階段昇降の障害の頻度のみ，sarcopenic obesity の群が大きい（36.8% vs 61.5%，P<0.05）という結果が得られた．

一方，筋力で定義した sarcopenic obesityの方がより機能予後との関連が出やすい．Finish health 2000 Survey では握力の低下と肥満が重なるとより歩行障害をおこした[13]．CHIANTY 研究では多変量解析で他の交絡因子を調整すると，筋肉量ではなくて，歩行速度が死亡の予知因子となった[14]．

Sarcopenic obesity と心血管障害

Sarcopenic obesityはインスリン抵抗性が強く，心血管疾患のリスクとなることが考えられるが，心血管疾患との関連を示した論文はほとんどない．NHANES III 研究では Sarcopenic Obesityはインスリン抵抗性増加や慢性の高血糖と関連を示し，65 歳未満でこの関連が強かった[15]．Korean Longitudinal Study on Health and Aging では appendicular skeletal mass/体重でサルコペニアを定義し，肥満を CT における内臓脂肪面積 100 cm^2 以上と定義すると，Sarcopenic obesityは単なる肥満やサルコペニアと比べてメタボリックシンドロームのリスクが高いと報告している[16]．高齢者 3,366 名の 8 年間の追跡調査では，ウエスト周囲径と筋力で定義した Sarcopenic obesityは心血管疾患のリスクが単なる肥満やサルコペニアと比べて高く，1.23 倍のリスクがあると報告している[17]．

サルコペニアと sarcopenic obesityとの相違

DXA 法による RSMI をサルコペニアの指標，lean mass/fat mass を sarcopenic obesity の指標として，年齢，骨密度，血清アルブミン，Hb，尿 CPR，HOMA-IR，収縮期血圧，拡張期血圧，HbA1c，中性脂肪値との Spearman の相関を見て，比較検討を加えてみた．表2に示すように RSMI は年齢，骨密度，血清 Alb，Hb，尿 CPR，収縮期血圧との有意の相関があり，サルコペニアは加齢とともに増え，骨密度低下，低栄養，収縮期高血圧と関連し，インスリン欠乏とも関連が見られ，一連の加齢現象の一つと考えられた．一方，lean mass/fat mass は

HOMA-IR，尿CPR，Hb，拡張期血圧と負の相関を示した．即ち，sarcopenic obesityは年齢とは関連せず，インスリン抵抗性，高インスリン血症，多血症，拡張期高血圧と関連し，肥満の病気としての特徴を大きく反映している．

サルコペニア，sarcopenic obesityと転倒について

外来糖尿病患者63名（年齢：78.4±6.0歳，男15例，女性48例）を対象にsarcopenic obesityと過去1年間の転倒回数，身体能力との関連を検討した．対象のBMIは23.2±2.9，罹病年数は17±8年，HbA1cは6.9±0.9%，治療法は食事のみ11名，経口薬45名，インスリン7例であった．Sarcopenic obesityの指標であるlean mass/fat massは握力（r＝0.255，P＜0.05）や開眼片足時間（r＝0.291，P＜0.05）と相関を示したが，転倒回数，老研式活動能力指標とは有意の関連を認めなかった．筋量を示すRSMIは握力（r＝0.530，P＜0.01）とは相関を示したが，転倒の回数，老研式活動能力指標とは相関を示さなかった．これに対してUp & Goテストの時間は転倒回数（r＝0.247，P＜0.001），老研式活動能力指標（r＝－0.439，P＜0.001）と有意の相関を示した．この結果はsarcopenic obesityや単なる筋肉量よりも筋肉の機能である身体能力の方が転倒，IADLの障害との関連が大きいことを示している．最近，サルコペニアの定義に6m歩行時間，椅子立ち上がり時間，立位バランス，Up & Goテスト，握力などの筋肉の機能（身体能力）も含めることが提唱されている[4]．したがって，sarcopenic obesityも筋肉の機能を考慮した定義によって見直す必要があり，機能的予後，転倒，死亡との関連があるか否かを再検討すべきである．

COI等：本論文に関連して，開示すべきCOIはなし．

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Preliminary communication

A tomato-rich diet is related to depressive symptoms among an elderly population aged 70 years and over: A population-based, cross-sectional analysis

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ABSTRACT

Background: Enhanced oxidative stress or defective anti-oxidant defenses are related to the pathogenesis of depressive symptoms. Lycopene is the most powerful antioxidant amongst the carotenoids. The aim of this study was to investigate the relationship between different vegetables, including tomatoes/tomato products (a major source of lycopene), and depressive symptoms in a community-based elderly population.

Methods: We analyzed a cross-sectional survey including 986 community-dwelling elderly Japanese individuals aged 70 years and older. Dietary intake was assessed using a valid self-administered diet-history questionnaire, and depressive symptoms were evaluated using the 30-item Geriatric Depression Scale with 2 cut-off points: 11 (mild and severe) and 14 (severe) or use of anti-depressive agents.

Results: The prevalence of mild and severe and severe depressive symptoms was 34.9% and 20.2%, respectively. After adjustments for potentially confounding factors, the odds ratios of having mild and severe depressive symptoms by increasing levels of tomatoes/tomato products were 1.00, 0.54, and 0.48 (p for trend <0.01). Similar relationships were also observed in the case of severe depressive symptoms. In contrast, no relationship was observed between intake of other kinds of vegetables and depressive symptoms.

Limitations: This is a cross-sectional study, and not for making a clinical diagnosis of depressive episodes.

Conclusions: This study demonstrated that a tomato-rich diet is independently related to lower prevalence of depressive symptoms. These results suggest that a tomato-rich diet may have a beneficial effect on the prevention of depressive symptoms. Further studies are needed to confirm these findings.

1. Introduction

For several decades, the health burden of stress-related diseases, including depressive symptoms and anxiety disorders, has been rapidly increasing. The presence of depressive symptoms in later life is recognized as a public health problem. Depressive symptoms contribute a significant independent risk for the onset of coronary disease (Wulsin and Singal, 2003), and disease susceptibility (Zorrilla et al., 2001). Depressive symptoms also worsens the outcomes of many medical disorders, promotes disability and increases mortality (Alexopoulos, 2005).

Several studies have suggested that enhanced oxidative stress or defective antioxidant defenses may be related to affective disorder or the pathogenesis of depressive symptoms (Bilici et al., 2001; Khanzode et al., 2003; Ozcan et al., 2004; Srivastava et al., 2002;

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Tsuboi et al., 2004). A longitudinal study in elderly residents showed preventive effects of vitamin E, a dietetically anti-oxidative compound, on the progression of depressive symptoms in male participants (Shibata et al., 1999). On the other hand, lycopene, a carotenoid antioxidant, is the most powerful antioxidant amongst carotenoids and there is no evidence of toxic effects (Heber and Lu, 2002). In vitro study of singlet oxygen quenching action, lycopene was shown to be 100 times more efficient than vitamin E (Atessahin et al., 2005). Thus, we hypothesized that a tomato-rich diet, a major source of lycopene (tomatoes and tomato-based sauces, juices, and ketchup account for more than 85% of the dietary intake of lycopene for most people (Rao and Rao, 2007)) may have a potentially beneficial effect on the prevention of depressive symptoms. However, to our knowledge, only a few studies have investigated the relationship between tomato/lycopene and depressive symptoms (Tsuboi et al., 2004). Moreover, no studies have fully investigated the relationship between a tomato-rich diet and depressive symptoms in a community-dwelling elderly population.

Because vegetables are good sources of antioxidant phytochemicals that mitigate the damaging effect of oxidative stress, we designed a cross-sectional study to compare the relationship between intake of several vegetables and tomato products with depressive symptoms in community-dwelling elderly participants aged ≥ 70 years.

2. Methods

2.1. Study participants

The Tsurugaya Project included subjects aged 70 years and older who were living in the Tsurugaya area of Sendai, one of the major cities in the Tohoku area of Japan. The data were obtained in 2002 from 1178 individuals giving their informed consent for data analysis. A detailed description of the methods has been published elsewhere (Niu et al., 2005a). The protocol of this study was approved by the Institutional Review Board of the Tohoku University Graduate School of Medicine.

In this study, depressive symptoms were assessed with the aid of the Geriatric Depressive symptoms Scale (GDS) (Brink et al., 1982). Of the 1178 subjects, 1169 completed the GDS. We also excluded those subjects whose did not have any information on diet ($n=94$). Furthermore, those who reported a history of cancer ($n=89$) and cognitive dysfunction (Mini Mental State Examination [MMSE] Score (Folstein et al., 1975) <18) ($n=17$) were also excluded. As a result of these exclusions, the final study population included 986 subjects.

2.2. Assessment of depressive symptoms

Depressive symptoms were assessed according to the Japanese version (Niino et al., 1991) of the 30-item GDS using 2 cut-off points (GDS score, ≥ 11 or 14) or the use of anti-depressive agents, indicating relatively mild to severe depressive symptoms or severe depressive symptoms (Brink et al., 1982).

2.3. Assessment of dietary intake

A brief self-administered diet history questionnaire (BDHQ) included 75 food items with specified serving sizes that were described by natural portions or standard weight and volume measures of the servings commonly consumed in this study population. For each food item, participants indicated their mean frequency of consumption over the past year, in terms of the specified serving size by checking 1 of the 7 frequency categories ranging from "almost never" to "2 or more times/d". The question of tomatoes/tomato products included some commonly eaten tomato foods such as tomato, tomato ketchup, stewed tomato, or tomato stew. According with BDHQ, Other kinds of vegetables were divided into four categories as follow: (1) Green-leaf vegetables, (2) Cabbage and Chinese cabbage, (3) Carrot, onion, burdock, lotus root and pumpkin, (4) Japanese white radish (daikon) and turnips. The mean daily intake of nutrients was calculated using an *ad hoc* computer program developed to analyze the questionnaire. The Japanese food composition tables, 4th edition, and the other sources (Sakai et al., 1995) were used as the nutrient database. The reproducibility and validity of the BDHQs have been described in detail elsewhere (Sasaki, 2005).

2.4. Assessment of other variables

Anthropometrics (height, body weight) were recorded using a standardized protocol. Body mass index (BMI) was calculated as weight (kg)/height^2 (m^2). Blood pressure (BP) was measured at home using an HEM747IC device (Omron Life Science Co. Ltd, Tokyo, Japan), which uses the cuff-oscillometric method to generate a digital display of systolic and diastolic pressures. The mean of 15.6 ± 10.5 (mean $\pm$ SD) BP measurements was used as the BP value. Participants who did not measure home BP for at least 3 days were treated as having missing information on hypertension. Hypertension was defined as a home systolic BP ≥ 135 mm Hg or a home diastolic BP ≥ 85 mm Hg or the use of antihypertensive agents (Chobanian et al., 2003).

Blood samples were drawn from the antecubital vein of the seated subject with minimal tourniquet use. Specimens were collected in siliconized vacuum glass tubes containing sodium fluoride for blood glucose, and no additives for lipids analyses. Blood glucose concentrations were measured using enzymatic methods (Shino-Test, Tokyo, Japan). Diabetes was defined as a casual blood glucose concentration of ≥ 200 mg/dL or the current use of antidiabetic medication.

Sociodemographic variables including gender, age, educational level, and perceived social support (PSS) were also assessed. Educational level attained was assessed by determining age at completion of schooling and was divided into 2 categories: ≤ 12 or >12 years. PSS was evaluated on the basis of responses ("yes" or "no") to the following 5 questions: "Do you have someone to whom you can talk when you are in trouble?" (PSS1); "Do you have someone to whom you can talk when your physical condition is not good?" (PSS2); "Do you have someone who can help you with daily housework" (PSS3); "Do you have someone who can take you to hospital when you do not feel well?" (PSS4); and "Do you have someone who can take care of you when you are ill in bed?" (PSS5). These questions were extracted from a previous study regarding social support and elderly depressive symptoms in a rural community (Muraoka et al., 1996). A single summed score was calculated based on the PSS 1–5. The lack of PSS was defined as PSS score=0.

Health-related variables assessed included history of physical illness, pain, cognitive function, instrumental activities of daily living (IADL), and current use of medication. History of physical illness was evaluated on the basis of responses ("yes" or "no") to questions. Pain within the previous 4 weeks was assessed by the question, "Have you had any pain recently? If so, how intensely do you feel such pain?" Possible answers were "no pain," "very mild pain," "mild pain," "moderate pain," and "severe pain." A subject who reported "mild" to "severe" pain was considered to have pain. Cognitive function was assessed on the basis of the MMSE and was classified into 2 categories: 18–23 and ≥ 24. IADLs were assessed using the Rouken–Shiki scale (Koyano et al., 1987) and a cut-off point of 10/11 was used to determine

impairment in IADL. The drug information was confirmed by a well-trained pharmacist.

Information on smoking status and drinking status were obtained from the questionnaire survey. Physical activity (PA) was assessed first by a self-reported single-item question on whether the participant undertook any PA during the past year. If yes, questions were asked about the frequency and duration of walking, brisk walking, and sports. PA was then classified into 3 categories, based on frequency and duration: (1) "High," at least 3–4 times per week for at least 30 min each time; (2) "Low," reporting some activity in the past year, but not enough to meet high levels; and (3) "None," no PA. Furthermore, PA was classified into 6 levels based on the above 3 categories and the type of physical activity, such as walking, brisk walking, and sports: (1) "Level 1," no walking, no brisk walking, no sports; (2) "Level 2," low walking, no brisk walking, no sports; (3) "Level 3," high walking, no brisk walking, no sports; (4) "Level 4," any walking, low brisk walking, no sports; (5) "Level 5," any walking, high brisk walking, no sports; (6) "Level 6," any walking, any brisk walking, low or high sports. Detailed information has been provided in previous reports (Niu et al., 2005b). Finally, subjects were divided into 2 categories: ≤ level 3 or > level 3.

2.5. Statistical analysis

Descriptive data are presented as mean (95% confidence interval [95% CI]) or percentages. Depressive symptoms were used as the dependent variable and the tomato/tomato product and other vegetable intake level as the independent variable. Multiple logistic regression analysis was used to examine the relationship of tomato/tomato product and other vegetable intake with depressive symptoms after adjustment for age, sex, BMI, hypertension, diabetes, history of cardiovascular diseases, smoking and drinking habits, physical activity, cognitive status, impaired IADL, self-reported body pain, educational level, living alone, marital status, lack of PSS, total energy intake, and intake of all kinds of fruits (tertiles), green tea (tertiles) (Niu et al., 2009), and mutual other kinds of vegetables. The odds ratios (ORs) and 95% CIs for depressive symptoms for increasing tomato/tomato product and other vegetable intake levels, with the lowest level as the reference, were also calculated using multiple logistic regression analysis. Interactions between tomato/tomato product and other vegetable intake levels and confounders of depressive symptoms were tested by the addition of cross-product terms to the regression model. A significant difference was defined as $p < 0.05$. All statistical analyses were performed using a Statistical Analysis System 9.1 edition for Windows (SAS Institute Inc., Cary, NC, USA.).

3. Results

Among 986 subjects who were available to be analyzed, 34.9% and 20.2% were classified as having mild and severe and severe depressive symptoms, respectively.

Age- and sex-adjusted participant characteristics according to tomato/tomato product status are presented in Table 1. The proportion of male, current smoker, lower educational level, and widowed or divorced status were significantly lower across the tomatoes/tomato products groups (p for trend ≤ 0.03). The proportion of subjects who were married was significantly higher across the tomatoes and tomato products groups (p for trend = 0.04). Mean total energy intake was significantly higher across the tomatoes/tomato products groups (p for trend < 0.0001). The mean GDS score was significantly lower across the tomatoes/tomato products groups (p for trend < 0.0001). Otherwise, no significant difference

Table 1
Age- and sex-adjusted characteristics according to categories of tomato/tomato product consumption.

	Tomatoes/tomato products consumption			p for trend
	≤ 1 time (wk)	2–6 times (wk)	≥ 1 time (d)	
No.	139	325	522	–
Age (year)	75.5 (74.7–76.3)	75.9 (75.4–76.4)	76.1 (75.7–76.5)	0.45
Sex (male)	49.6	48.3	36.2	< 0.001
BMI (kg/m^2)	23.5 (23.0–24.1)	23.8 (23.5–24.2)	23.9 (23.6–24.2)	0.42
Diabetes	7.9	9.2	9.4	0.70
Hypertension	71.2	68.6	69.0	0.62
History of CVD	14.4	16.0	14.8	0.80
Smoking status	–	–	–	–
Current smoker	25.9	12.9	9.8	< 0.001
Ex-smoker	26.6	35.1	25.9	0.41
Drinking status	–	–	–	–
Current drinker	44.6	44.3	35.8	0.32
Ex-drinker	9.4	12.0	12.3	0.17
PA (> level 3)	38.1	37.9	37.9	0.60
Self-reported total number of physical illness (≥ 2)	63.3	68.6	69.9	0.26
Cognitive ability (18 ≤ MMSE < 24)	5.8	9.9	7.1	0.61
Impaired IADL	12.2	14.2	10.5	0.19
Self-rated health (yes)	79.1	82.5	81.8	0.44
Body pain (yes)	70.5	81.2	77.4	0.23
Lack of PSS (total score=0)	15.1	14.8	13.4	0.34
Educational level (≤ 12 years)	79.1	71.1	67.8	< 0.001
Living alone (yes)	28.1	21.5	25.1	0.13
Marital status married	59.0	63.4	60.5	0.04
Widowed or divorced	37.4	33.2	34.9	0.03
Total energy intake (kcal/d)	1841.7 (1768.4–1915)	1976.7 (1928.8–2024.6)	2084.4 (2045.8–2123)	< 0.0001
GDS	10.9 (10.1–11.8)	9.1 (8.5–9.7)	8.4 (7.9–8.8)	< 0.0001

BMI, body mass index; CVD, cardiovascular diseases; PA, physical activity; PSS, perceived social support; MMSE, Mini Mental State Examination; IADL, Instrumental Activity of Daily Living; GDS, Geriatric Depression Scale.
Variables are presented as mean (95% confidence interval).

Table 2
Adjusted association between consumption of tomatoes/tomato products and other kinds of vegetables and depressive symptoms [a].

Odds ratio (95% confidence interval)	Tomato and tomato product consumption			p for trend[b]
	≤1 time (wk)	2–6 times (wk)	≥1 time (d)	
Tomatoes and tomato products	–	–	–	–
No. of participants	139	325	522	–
No. of mild and severe depressive symptoms, defined as GDS of ≥11 or use of antidepressants	70	111	163	–
Crude	1.00	0.51 (0.34–0.77)	0.45 (0.31–0.66)	<0.001
Age- and sex-adjusted	1.00	0.49 (0.33–0.74)	0.40 (0.27–0.59)	<0.0001
Multiple adjusted [c]	1.00	0.54 (0.35–0.85)	0.48 (0.31–0.75)	<0.01
Green-leaf vegetables	–	–	–	–
No. of participants	188	523	275	–
No. of mild and severe depressive symptoms, defined as GDS of ≥11 or use of antidepressants	80	179	85	–
Crude	1.00	0.70 (0.50–0.99)	0.60 (0.41–0.89)	0.01
Age- and sex-adjusted	1.00	0.69 (0.49–0.97)	0.58 (0.39–0.85)	<0.01
Multiple adjusted [c]	1.00	0.78 (0.51–1.19)	0.72 (0.45–1.15)	0.19
Cabbage and Chinese cabbage	–	–	–	–
No. of participants	200	605	181	–
No. of mild and severe depressive symptoms, defined as GDS of ≥11 or use of antidepressants	78	203	63	–
Crude	1.00	0.79 (0.57–1.10)	0.84 (0.55–1.27)	0.37
Age- and sex-adjusted	1.00	0.78 (0.56–1.09)	0.79 (0.51–1.20)	0.24
Multiple adjusted [c]	1.00	1.07 (0.71–1.64)	1.46 (0.85–2.50)	0.18
Carrot, onion, burdock, lotus root and pumpkin	–	–	–	–
No. of participants	102	556	328	–
No. of mild and severe depressive symptoms, defined as GDS of ≥11 or use of antidepressants	42	199	103	–
Crude	1.00	0.83 (0.60–1.15)	0.61 (0.41–0.92)	0.02
Age- and sex-adjusted	1.00	0.78 (0.56–1.09)	0.56 (0.37–0.85)	<0.01
Multiple adjusted [c]	1.00	1.31 (0.77–2.27)	1.34 (0.74–2.45)	0.44
Japanese white radish (daikon) and turnips	–	–	–	–
No. of participants	265	519	202	–
No. of mild and severe depressive symptoms, defined as GDS of ≥11 or use of antidepressants	105	178	61	–
Crude	1.00	0.80 (0.59–1.08)	0.66 (0.45–0.97)	0.03
Age- and sex-adjusted	1.00	0.78 (0.57–1.06)	0.61 (0.41–0.90)	0.01
Multiple adjusted [c]	1.00	0.94 (0.65–1.37)	0.70 (0.43–1.13)	0.17

[a] GDS, Geriatric Depression Scale.
[b] Obtained by using multiple logistic regression analysis.
[c] Adjusted for age, sex, BMI, hypertension, diabetes, history of cardiovascular disease, smoking and drinking habits, physical activity, cognitive status, impaired instrumental activities of daily living (IADL), self-reported body pain, educational level, living alone, marital status, lack of perceived social support (PSS), total energy intake, all kinds of fruits, green tea, and mutual other kinds of vegetables.

was observed among tomatoes/tomato products groups (p for trend ≥0.13).

Table 2 shows the adjusted relationship between tomatoes/tomato products and other kinds of vegetables and mild and severe depressive symptoms. The ORs for mild and severe depressive symptoms decreased across the levels of tomato/tomato product intake. Age- and sex-adjusted ORs (95% CI) for depressive symptoms across tomato/tomato product intake levels were 1.00, 0.49 (0.33–0.74), and 0.40 (0.27–0.59) (p for trend <0.0001). These results were unchanged when adjusted for multiple confounding factors. Similar relationships were also observed when males and females were analyzed separately (p for interaction=0.08). Of the other covariants, smoking/drinking status and educational level were related with depressive symptoms. The tests for interactions between the categories of tomato/tomato product intake and these potential confounders in the final models were not found to be significant. Furthermore, because depressive status is also related to unhealthy eating habits and appetite (Andreasson et al., 2007; Cassano and Fava, 2002), a sensitivity analysis was added to assess the relationship between tomatoes/tomato products and depressive symptoms, excluding those who had very low (under 2.5%) or high (upper 2.5%) energy intake. However, this exclusion did not change the above results. Similar results were also observed when a cut-off of ≥14 or the use of antidepressants was used to indicate severe depressive symptoms. In the final model, the ORs (95% CI) for severe depressive symptoms across tomato/tomato product intake levels were 1.00, 0.64 (0.39–1.08), and 0.60 (0.37–0.99). In contrast to tomato/tomato product intake, no relationship was observed between intake of other kinds of vegetables and the prevalence of depressive symptoms (Table 2). Similar results were also observed when a cut-off of ≥14 or the use of antidepressants was used to indicate severe depressive symptoms (data not shown).

4. Discussion

This study examined the relationship between the intake of various vegetables, including tomatoes/tomato products, a main source of lycopene, and depressive symptoms among a community-dwelling elderly population aged 70 years and over. These results suggest that a high intake of tomatoes/tomato products was independently related to a lower prevalence of depressive symptoms. In contrast to tomato/tomato product intake, no relationship was observed between intake of other kinds of vegetables and depressive symptoms.

In this study, we have hypothesized that the intake of tomatoes/tomato products may have a potentially beneficial effect on the prevention of depressive symptoms. Although several studies have investigated the relationship between dietary antioxidant nutrients, such as folic acid and vitamin E, and depressive symptoms, few studies have reported the relationship between intake of tomatoes/tomato products and depressive symptoms (Alpert et al., 2000; Maes et al., 2000; Miyake et al., 2006; Shibata et al., 1999; Tsuboi et al., 2004). Only one study has assessed the correlations between serum lycopene and depressive score, in subjects consisting of 66 healthy female volunteers aged 38–70 years (Tsuboi et al., 2004). However, in that study, many confounding factors were not considered and the results have not suggested a significant correlation between lycopene and depressive score. In this larger community-based population study we adjusted for a considerable number of confounding factors. The current results suggest that high tomato/tomato product intake levels are independently related to a lower prevalence of depressive symptoms. Moreover, we also conducted a stratified analysis for sex. Similar relationships were also observed when males and females were analyzed separately.

Lycopene is the red-colored carotenoid predominantly found in tomatoes, but in few other fruits or vegetables (Bramley, 2000). Lycopene has the strongest antioxidant activity of various common carotenoids (Di Mascio et al., 1989). Oxidative stress may accelerate aging and increase the risk of chronic diseases, such as coronary heart disease, cancer, and rheumatoid arthritis; dietary intake of tomatoes/tomato products containing lycopene have been shown to be related to decreased risk of these chronic medical illnesses (De Pablo et al., 2007; Heber and Lu, 2002). Since these chronic medical illnesses are also related to the occurrence of depressive symptoms, particularly in elderly people, the presence or degree of these chronic medical illnesses may be a potential mechanism linking intake of tomatoes and tomato products to depressive symptoms. Furthermore, since enhanced oxidative stress or defective antioxidant defenses may be related to depressive symptoms, lycopene may directly link tomato and tomato product intake to depressive symptoms because of their anti-oxidative effect. Further study is needed to confirm these findings.

In the present study, lycopene concentration from tomatoes/tomato products was not calculated. In fact, food frequency questionnaires generally used in epidemiological studies vary greatly in their usefulness in estimating the true variation in lycopene intake among individuals. A review indicated that dietary intake of tomato/lycopene is difficult to quantify precisely for several reasons: different food habits, inaccurate estimation of dietary intake, the quality of the food database used, and variation of lycopene concentration within a given food (Porrini and Riso, 2005). Moreover, since lycopene is predominantly found in tomato and tomato-based products (at least 85%) (Bramley, 2000), but only in a few other fruits or vegetables (e.g., watermelon, pink grapefruit, guava, and papaya), the frequency of eating tomatoes/tomato products was used to assess the relationship between tomatoes/lycopene and depressive symptoms in this study.

This study had several limitations. First, the GDS has been designed for measuring the intensity of depressive symptoms and not for making a clinical diagnosis of depressive episodes. Therefore, a larger sample population using a standardized comprehensive structured diagnostic interview should be studied to confirm the effect of depressive symptoms on functional decline. Second, because this study was a cross-sectional study, we could not conclude that lower tomato and tomato product intake increased the occurrence of depressive symptoms or that depressive symptoms lead to a decline in tomato/tomato product intake. Therefore, a prospective study or trial should be undertaken to confirm the relationship between tomato/tomato product intake and depressive symptoms. Moreover, although we adjusted for a considerable number of confounding factors, we cannot exclude the possibility that depressive symptoms are affected by other dietary habits correlated with habitual dietary intake of tomatoes/tomato products. Therefore, an intervention study is necessary to establish a causal relationship between tomato/tomato product intake and depressive symptoms.

In conclusion, this study demonstrated that the intake level of tomatoes/tomato products, as measured by a self-administered questionnaire, is independently related to a lower prevalence of depressive symptoms in a community-dwelling older population. These results suggest that a tomato-rich diet may have a beneficial effect on the prevention of depressive symptoms. Further studies are needed to confirm these findings.

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Nothing declared.

Conflict of interest

All the authors have no conflicts of interest exists to disclose.

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OBSERVATIONS

Sitagliptin Successfully Ameliorates Glycemic Control in Werner Syndrome With Diabetes

Werner syndrome (WS) is an autosomal recessive disorder caused by a mutation in the *WRN* gene, and it is considered to be a representative type of progeroid syndrome (1). Patients with WS often exhibit insulin resistance, which is associated with the accumulation of visceral fat and disadipocytokinemia. We and others have previously reported that pioglitazone, a peroxisome proliferator–activated receptor γ ligand, improved glycemic control and insulin sensitivity with normalization of disadipocytokine levels in patients with WS (2,3).

Here we describe a diabetic subject with WS that had good glycemic control with pioglitazone initially but worsened because of abdominal obesity and increasing visceral fat area. Sitagliptin, an inhibitor of dipeptidyl peptidase-4, was then administered, which resulted in successful improvement of glycemic control.

A 58-year-old Japanese woman with WS was admitted to our hospital with poor glycemic control. At the first visit to our hospital at 46 years of age, she exhibited graying and loss of hair, short stature, a hoarse voice, refractory skin ulcers, bilateral juvenile cataracts, dyslipidemia, and diabetes. The diagnosis of WS was confirmed by genomic DNA analysis. At that time, her height was 1.46 m, weight was 36 kg, and BMI was 15.1 kg/m^2. Her visceral fat area was 111 cm^2 (normal range, <100 cm^2 for Japanese). She was prescribed 15 mg pioglitazone daily, which resulted in stable glycemic control. Her glycated hemoglobin (HbA_{1c}) level was maintained at ~6.9% for 12 years. However, she gradually gained weight and visceral fat area (191 cm^2), which worsened her glycemic control. At the present admission, continuous glucose monitoring system (CGMS) was performed, and postprandial hyperglycemia was observed. Therefore, a 50-mg daily dose of sitagliptin was added to the pioglitazone regimen. Her laboratory parameters before and after sitagliptin administration for 6 months were as follows: fasting glucose, 122 and 110 mg/dL; 2-h postprandial glucose, 162 and 129 mg/dL; fasting C-peptide, 2.81 and 3.32 mg/dL; 2-h postprandial C-peptide, 13.99 and 11.5 mg/dL; HbA_{1c}, 7.5 and 6.5%; and mean ± SD of glucose levels detected by CGMS, 163.2 ± 32.0 and 117.1 ± 20.6 mg/dL, respectively. CGMS confirmed that sitagliptin effectively suppressed postprandial hyperglycemia.

Although patients with WS are insulin resistant, it was suggested that only those who have impaired insulin secretion develop overt diabetes (4). We were unable to observe an improvement in 2-h postprandial C-peptide levels after sitagliptin administration; nevertheless, sitaglipitin may have improved early insulin secretion in response to meals. Furthermore, sitagliptin reportedly suppresses glucagon secretion. Because hyperglucagonemia has been observed in patients with WS (5), sitagliptin may ameliorate glycemic controls at least in part via correction of dysglucagonemia.

In conclusion, we demonstrated that a single dose of sitagliptin was well tolerated in a patient with WS and diabetes, resulting in a significant improvement in glycemic control. Sitagliptin may represent an alternative choice for treatment of diabetes in patients with WS. Further studies on the use of dipeptidyl peptidase-4 inhibitor in WS with diabetes will confirm our findings.

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Brief report

Atorvastatin ameliorates podocyte injury in patients with type 2 diabetes complicated with dyslipidemia

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ABSTRACT

We examined the effects of atorvastatin on urinary podocyte excretion. Thirteen patients with type 2 diabetes receiving 2.5 mg of rosuvastatin were recruited and the medication was switched to 10 mg of atorvastatin for a 24-week period. With the switch to atorvastatin, the urinary excretion of podocytes was significantly reduced.

1. Introduction

A number of clinical studies have indicated that the 3-hydroxyl-3-methylglutaryl-CoA (HMG-CoA) reductase inhibitor (statin) has favorable effects on renal function by controlling dyslipidemia [1–3]. Furthermore, it has been reported that various statins have a different impact on renal function, especially on diabetic nephropathy (DN) [4].

The detachment of podocytes from the glomerular basement membrane and podocyte loss in the urine are associated with glomerulosclerosis progression [5]. Therefore, monitoring urinary podocytes could be clinically useful [6].

With this in mind, we examined the effect of atorvastatin, a lipophilic statin, on urinary podocytes when rosuvastatin, a hydrophilic statin was switched for atorvastatin.

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2. Methods and research design

2.1. Subjects

Thirteen patients with type 2 diabetes (10 men and 3 women) were recruited in this study (Table 1). All patients had received 2.5 mg rosuvastatin for at least 3 months. We only recruited patients with normo- to microalbminuria and excluded those with macroalbuminuria, hematuria, and collagen diseases. We also recruited patients who were positive for the excretion of urinary podocytes.

2.2. Study design

Statin therapy of diabetic patients positive for the excretion of urinary podocytes was switched from 2.5 mg of rosuvastatin to 10 mg of atorvastatin for a 24-week period, and the effects on urinary podocyte excretion evaluated before and after switching the statin. The present study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by the ethical committee of the School of Medicine, Chiba University prior to its inception. All patients understood the study aims and methods and provided written, informed consent.

2.3. Clinical parameters of blood and urine

Venous blood samples and urine samples were collected at baseline and at the end of the intervention in the morning after a 12-h fast. Fresh samples of first-voided morning urine were collected and urinary podocytes were measured using the U-podocyte test (at Mitsubishi Chemical Medicine) as described previously [7].

Table 1 – Basic characteristics of patients.

Number (men/women)	13 (10/3)
Age (years)	61.3 ± 11.9
Systolic blood pressure (mmHg)	122.4 ± 16.9
Diastolic blood pressure (mmHg)	71.2 ± 1.0
Fasting blood glucose (mg/dl)	158.1 ± 64.4
HbA1c (mmol/mol)	53.7 ± 11.2
HbA1c (%)	7.06 ± 1.04
Serum creatinine (mg/dl)	0.82 ± 0.18
Estimated GFR (ml/min/1.73 m^2)	70.1 ± 19.2
Urinary albumin (μg/g Cre)	28.6 ± 21.4
Uric acid (mg/dl)	5.4 ± 1.6
LDL-C (mg/dl)	97.5 ± 21.9
HDL-C (mg/dl)	51.5 ± 12.1
TG (mg/dl)	169.2 ± 73.4
ARBs (%)	46.2
Sulfonylurea (%)	38.5
αGI (%)	46.1
Metformin (%)	61.5
Thiazolidine (%)	38.5
DPPIV-I (%)	38.6
Insulin (%)	30.7

LDL-C: low density lipoprotein cholesterol, HDL-C: high density lipoprotein cholesterol, ARB: angiotensin II type 1 receptor blocker, αGI: alpha glucosidase inhibitor, DPPIV-I: dipeptidyl peptidase IV inhibitor.

2.4. Statistical analysis

Values are indicated as mean ± standard deviation (SD). A paired t-test was used and statistical analyses were performed using SPSS 15.0J (SPSS Japan Inc., Tokyo, Japan). A p-value < 0.05 was considered statistically significant.

3. Results

3.1. Atorvastatin significantly reduces urinary podocyte excretion

As shown in Fig. 1, urinary podocytes were undetected in 10/13 (77%) of patients after a 24-week period of atorvastatin administration. During the study period, there was no change in treatment for diabetes mellitus or hypertension, and there was no difference in lipid levels, glucose metabolism, or blood pressures before or after the statin switch (Table 2). The mean values of the oxidative stress marker, urinary F(2)-isoprostane, tended to decrease without reaching significance. Also, there were no adverse effects and no significant differences in urinary albumin excretion (Table 2) and estimated glomerular filtration rate (eGFR) (Fig. 1) before and after the statin switch.

4. Discussion

In this study in people with type 2 diabetes and urinary podocyte excretion, switching from rosuvastatin to atorvastatin significantly reduced urinary podocyte loss.

A recent meta-analysis has shown that statin therapies can reduce proteinuria and benefit kidney function [1] however the effect varies between statins. For instance, high-dose atorvastatin significantly reduced proteinuria but did not affect renal function, whereas rosuvastatin was associated with a significant decline in renal function and had no effect on proteinuria in patients with type 2 diabetes and moderate

Table 2 – Clinical parameters of patients before and after switching medication to atorvastatin from rosuvastatin.

	Before	After 6 months	p-Value
Urinary podocytes (cells/ml)	0.3 ± 0.2	0.07 ± 0.16	0.002
Estimated GFR (ml/min/1.73 m^2)	70.1 ± 19.2	69.5 ± 20.2	0.94
Urinary albumin (μg/g Cre)	28.6 ± 21.4	30 ± 29.2	0.89
LDL-C (mg/dl)	97.5 ± 21.9	95.4 ± 29.0	0.84
HDL-C (mg/dl)	51.2 ± 10.2	51.5 ± 12.1	0.94
Triglyceride (mg/dl)	169.2 ± 73.4	153.2 ± 55.1	0.53
F(2)-isoprostane (pg/ml)	449.1 ± 175.8	408.5 ± 117.8	0.53
FBS (mg/dl)	158.1 ± 64.5	136.6 ± 44.3	0.33
HbA1c (mmol/mol)	53.7 ± 11.2	51.0 ± 7.7	0.24
HbA1c (%)	7.06 ± 1.04	6.4 ± 0.71	0.5
Systolic blood pressure (mmHg)	122.4 ± 16.9	126.2 ± 18.4	0.59
Diastolic blood pressure (mmHg)	71.2 ± 14.0	70.0 ± 13.5	0.83

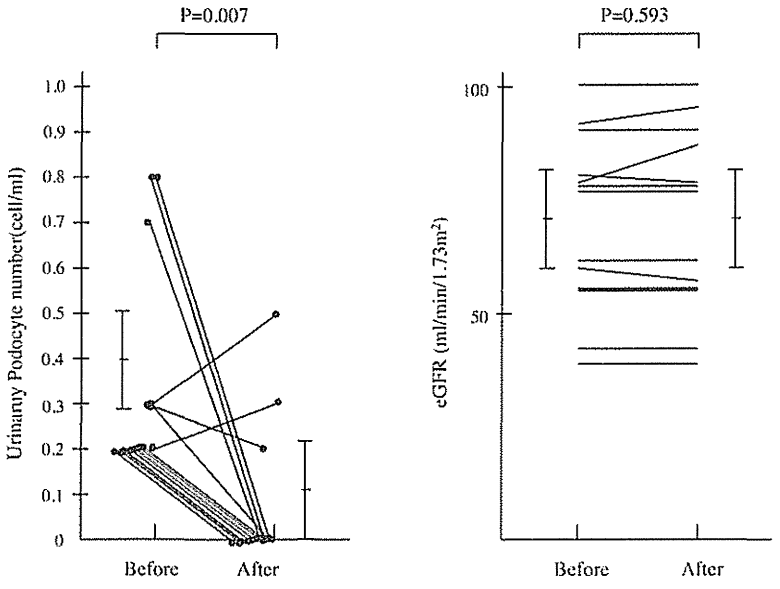

Fig. 1 – Effects of atorvastatin on urinary podocytes and estimated GFR Patients with urinary podocytes had their medications switched from 2.5 mg of rosuvastatin to 10 mg of atorvastatin for 24 weeks. The effects on urinary podocytes and eGFR were evaluated before and after switching the statins.

proteinuria [4]. Wu et al. reported that both atorvastatin and rosuvastatin improved glomerular filtration rate, whereas atorvastatin seemed to be more effective in reducing proteinuria in a meta-analysis of 16 clinical trials [8]. Our results also showed that atorvastatin seemed to be more protective for podocyte loss than rosuvastatin.

The role of podocytes in DN development has been thoroughly investigated and detection of urinary podocytes is a good marker for progression of several kidney diseases such as glomerulonephritis, IgA nephritis, focal glomerular sclerosis, and DN [6,7,9–11].

A protective role of statins on glomerular podocytes has also been demonstrated. Shibata et al. reported that fluvastatin suppressed puromycin aminonucleoside-induced activation of RhoA and actin cytoskeleton reorganization [12].

The renoprotective effects of statins are related to the pleiotropic effects beyond low density lipoprotein cholesterol (LDL-C) lowering effects. Statins vary differently in their rate of absorption, amount of protein binding, degree of renal excretion, metabolism and hydrophobicity. Small angle X-ray diffraction shows that statins distribute differently within cellular membranes because of minor variations in their chemistry, leading to differences in their efficacy and metabolism. Hydrophilic properties of rosuvastatin prevent access to the hydrophobic membrane hydrocarbon core. By contrast, atorvastatin intercalates into the upper hydrocarbon core of the membrane lipid bilayer adjacent to the glycerol backbone [13]. This membrane location may influence certain intracellular signaling processes in podocytes, particularly in membrane bound small GTPase which is important for podocyte cytoskeleton rearrangement [12].

Atorvastatin is a potent statin for lowering LDL-C and induces anti-oxidative stress [14]. Anti-oxidant therapy has been shown to reduce or retard damaging effects of ROS and diabetic complications [15,16]. Therefore, we examined levels of F(2)-isoprostane, a marker of oxidative stress, before and after switching statin medications, but were unable to detect any significant differences.

Although the occurrence of urinary podocytes was reduced by switching rosuvastatin to atorvastatin, we were not able to detect a significant difference in renal function such as eGFR and ACR. Because the metabolic parameters were already well controlled before switching the statins, not enough time may have passed, to detect a difference in renal function.

In conclusion, our results show that atorvastatin may protect people with type 2 diabetes from podocyte injury in addition to offering benefits of LDL-C lowering. However, large-scale population-based randomized controlled trials for longer periods of time are necessary to define the benefits of atorvastatin use in the patients with urinary podocyte excretion.

Conflict of interest

The authors declare that they have no conflict of interest.

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