(倫理面への配慮) 日常診療の範囲内で実施する。

C．研究結果

今回の研究では、NGT179 人のうち 58 人に 1 時間血糖値上昇(HG 群)を認め、NGT の約 33%を占めていた。Insulinogenic index は NGT、IFG、isolated IGT で LG 群 0.4 と比較して HG 群 0.2 と著明な低下を認めた。HOMA β-cell は NGT、isolated IGT で HG 群が LG 群と比較して有意な低下を認めた。HOMA-IR や ISI composite は NGT、IFG、isolated IGT は HG 群、LG 群間で有意な差は認めなかった。また負荷後 1 時間血糖値はインスリン分泌、抵抗性の指標の中で Insulinogenix index と最も強い相関を示した。

D．考察

日本人をはじめとするアジア人は欧米人と比較して BMI、インスリン抵抗性が低い反面、インスリン分泌能が低いことを特徴である。今回、負荷後 1 時間血糖値の上昇にはインスリン分泌、特にインスリンの初期分泌が重要な因子であることが証明された。また NGT の 33%に負荷後 1 時間血糖値の上昇とインスリン初期分泌低下を認めた。この結果は、インスリン抵抗性を主体とした欧米とは異なり，正常耐糖能でも既にインスリン分泌能の低下が存在していることを示唆している。

E．結論

OGTT 負荷後 1 時間血糖値の上昇にはインスリン分泌、特にインスリン初期分泌の低下が重要な因子である。

F．健康危険情報　なし

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H．知的財産権の出願・登録状況

1.特許取得　なし

2.実用新案登録　なし

3.その他　なし

wave velocity in nonobese Japanese patients with type 2 diabes mellitus.

平成１９年度厚生労働科学研究費補助金（社会保障国際協力推進研究事業）
分担研究報告書

食事の脂質と糖質の比率がベトナムの成人女性の食後血糖値に及ぼす影響

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山　本　　茂

要旨　　米の含有量の多い典型的なベトナムの食事が食後血糖値に及ぼす影響を明らかにする目的で本研究を行った。被験者は、BMI が近い 20、40 および 60 歳代（各年齢層 10 名）の健常な女性とした。タンパク質含量は 13-15%エネルギーで似ているが、脂肪と糖質のエネルギー比（FC 比）および野菜の量が異なる 4 種類の食事を交叉法で与えた。A 食はベトナムの一般的な食事で、FC 比は 14:71、米由来糖質は 84 g であった。B 食は、A 食に比べて脂肪割合を高く、糖質割合を低くした（FC 比 30:57）。C 食は野菜が無い以外は A 食と同じであった。エネルギー量は３食とも約 2.1MJ であった。D 食は、糖質は A 食と、脂肪は B 食と同量とし、FC 比は 26:61 で、エネルギー量は 2.4 MJ であった。試験食を摂取する前に、空腹時血糖値を測定した。食後 30 分ごとに２時間まで採血し、血糖値の変化を観察した。血糖値の変化を示した曲線下の面積(AUC)を計算し、４試験食で比較した。20 歳代では、AUC に有意差は見られなかった。40 歳代では、野菜のある A 食は、野菜のない C 食に比べて AUC の低い傾向がみられた(p=0.07)。60 歳代では、糖質の多い A 食の AUC は、糖質の少ない B 食より、有意に高かった(p<0.001)。食後血糖上昇は年齢に相関していたが(r=0.26, p<0.01)、BMI には相関しなかった(p=0.20)。食事中の脂肪の割合が高くなるほど、食後血糖上昇反応は低くなった(r=-0.28, p<0.01)。以上の結果、ベトナム人が通常摂取する食事は糖質が高く、特に高齢者の食後血糖値を上昇すること、および野菜は食後血糖値の上昇を抑制することが示唆された。

To elucidate the effect of a typical Vietnamese diet including high content of white rice on postprandial blood glucose levels, the present study was designed. Thirty healthy female subjects with similar body mass index, 10 each in their twenties, forties and sixties, were recruited. Four meals with similar protein energy percentage (13-15%) were designed according to the different energy ratio of fat and carbohydrate (FC ratio) and vegetable contents and given by cross-over design. Meal A was designed according to commonly consumed diet in Vietnam. The FC ratio was 14:71 and 84 g of carbohydrate was from rice. Meal B contained carbohydrate in a less ratio than meal A by fat replacement and its FC ratio was 30:57. Meal C was similar to meal A except lacking vegetables. Energy of meal A, B and C were about 2.1 MJ. Meal D was designed to match the amount of carbohydrate and fat within A and B, respectively. The FC ratio of meal D was 26:61 and energy was about 2.4 MJ. Fasting blood glucose was measured before consumption of a test meal. Postprandial blood glucose was measured every 30 min for 2 h. Areas under the curve (AUC) were calculated to compare the glycemic response among the four test meals. There was no significant difference in AUC among the four test meals in the subjects of twenties. In the subjects of the forties, the AUC of meal A tended to be lower than that of meal C (p=0.07). In the subjects of sixties, the AUC of meal A was significantly higher than that of meal B (p<0.001). Glycemic responses showed a significant relationship with age (r=0.26, p<0.01); however, there was no association between glycemic responses and BMI (p=0.20). Dietary fat ratios were inversely associated with glycemic responses (r=-0.28, p<0.01). In conclusion, the diet with about 70% energy from carbohydrate which is commonly consumed by Vietnamese may increase glycemic response, especially in the elderly people and dietary vegetable may be beneficial to prevent such an increase in glycemic response.

A．研究目的

Introduction

Evidences showed increasing prevalence of diabetes in Asian population and also indicated the risk of diabetes in Asians may be higher than that of other racial groups at the same body mass index (BMI) (*1-6*). The use of white rice as a staple food, since white rice has been demonstrated and classified as high glycemic index (GI) food, has been considered as a risk factor for diabetes (*5-7*).

Walter Willett (*8*) and colleagues proposed a "Healthy Eating Pyramid" recently which suggested refined carbohydrates, such as white rice, should be used sparingly as are sweets. Plant oil was suggested to be near the foundation of the pyramid to meet the fact that Americans get 35% or more of daily energy from fat. Based on evidences, plant oil contained a plenty of polyunsaturated fatty acid which was considered superior than animal fat (*8*). It has been considered that the prevalence of diabetes increased severely in the past years because Americans consumed too much carbohydrate instead of fat, following the "Food Guide Pyramid" published in 1992 (*9*). The suggestions to use white rice sparingly (*8*) may bring a great impact on the dietary culture of Asians.

Compared with America, fat intake ratio was low in Asian countries, especially in Vietnam. According to the National Nutrition Survey in Vietnam, energy from protein, fat, and carbohydrate (PFC ratio) were 13%, 12%, and 75%, respectively (*10*). Some rural regions in Vietnam were reported to get more than 80% of their energy intake from carbohydrate (*10*). We hypothesized that the use of rice as a staple food is not the only risk factor for diabetes as there might be a synergistic effect with others among which is a deficient ratio of macronutrients. Though rice had been classified as high-GI food, most of the time individuals do not eat rice only but combine them in mixed meals. Some researchers also suggested that consuming single food with other dishes have lower GI value than consuming single food only (*11, 12*). Glycemic load (GL) was then introduced to represent the combination of quality and quantity of carbohydrate consumed (*13*). However, the utility of GI/GL was still controversial (*12, 13*). Review of literatures indicated the dietary GI or GL was used as a measure of glycemic response on young subjects or diabetes patients (*13 —15*). There have been no adequate studies on comparison of postprandial glycemic responses among the young and the elder healthy subjects.

This study was aimed to provide data on postprandial glycemic responses based on Vietnamese common diet with high carbohydrate intake by involving three different age groups.

B．研究方法

Methods and Materials

Subjects

This study was conducted in Khanh Van Commune, Ninh Binh Province, Vietnam. Healthy female subjects of three age groups with similar BMI (those in the twenties, forties and sixties) were recruited from a pool of farmers and participated after harvesting season. Ten subjects were enrolled in each group. Hypertension, hyperlipidemia, diabetes, impaired fasting glucose, alcohol-drinking, and smoking were exclusion criteria. Self-monitored blood glucose device (SMBG device, Precision Xtra, Abbott Laboratories, Abbott Park, Illinois, U.S.A.) was used to measure blood glucose for screening. Fasting blood glucose more than 110 mg/dl was excluded according to American Diabetes

Association's (ADA) criteria (*16*). Height and weight were measured to 0.1 cm and 0.1 kg, respectively, using a digital weight balance and height scale.

Test meals

Four test meals (A, B, C and D) were designed using white rice as a staple food and pork meat with or without vegetable as side dishes. Seasonings were almost the same for all the meals. Composition of test meals is shown in Table 1. Since the purpose of this study was to elucidate the effect of dietary FC ratio, the proportion of energy from protein of the four test meals was kept relatively constant (13% - 15%). Meal A was designed to be a Vietnam common diet according to the National Nutrition Survey of Vietnam (*10*). Its FC ratio and energy intake were as commonly consumed in Vietnam. Total energy of meal A, B and C were about 2.1 MJ. FC ratios in test meals A and B were 14:71 and 30:57, respectively. Studies also indicated that dietary vegetable improved glycemic control by reducing or delaying the absorption of carbohydrate (*17-20*). Meal C was designed to be similar to meal A except lacking vegetables and its FC ratio was 15:71. To elucidate whether glycemic response was also influenced by a deficient FC ratio, not only because of the amount of carbohydrate, meal D was designed to match the amount of carbohydrate and fat within A and B, respectively. Total energy of meal D was 2.4 MJ with FC ratio of 26:61. Energy intake and food composition were determined by Nutritive Composition Table of Vietnamese Foods (*21*). All test meals were measured, prepared and divided into portions in each morning.

(倫理面への配慮)

Informed consent was received from all subjects and approval for the study was given by the Ethical Committee of Ministry of Health, National Institute of Nutrition, Vietnam.

Table 1. Dietary composition and PFC ratios of four test meals

	Meal A*	Meal B	Meal C	Meal D
White Rice (g)	110	86	110	110
Oil (g)	4	13	4	13
Pork lean (g)	40	40	40	40
Vegetable(g; cabbage)	100	100	0	100
Fish sauce (g)	5	5	5	5
Protein (g)	18.4	16.5	16.6	18.4
Fat (g)	7.9	16.7	7.9	16.9
Carbohydrate (g)	89.2	70.9	83.8	89.2
Fiber (g)	2.0	1.9	0.4	2.0
P:F:C ratio	15:14:71	13:30:57	14:15:71	13:26:61
Total energy (MJ)	2.1	2.1	2.0	2.4

*Meal A was designed to be a Vietnam common diet.
(1 kcal = 4.186 kJ)

Study design and blood glucose measurement

Each subject took the 4 test meals in separate mornings by cross-over design. Subjects were asked to fast before testing for at least 10 h. Nothing was allowed to eat or drink except water. In the test morning, the subjects arrived at the local health center with least strenuous means of transportation. After resting in a comfortable position for at least 10 min, body weight was measured. Fasting blood glucose was measured before consumption of test meal. Test meals were consumed within 15 min. Postprandial blood glucose was measured every 30 min for 2 h from the consumption of the test meals. The incremental area under the curve (AUC) changes in blood glucose was computed by the trapezoidal method (*22*). The AUC for each test meal was expressed as glycemic response for 2 h. AUCs of the four test meals among the three age groups were compared. The blood glucose was measured using a SMBG device. This biosensor glucose test strip is based on an electron-transferred glucose oxidase reaction (*23*). A fill trigger electrode was designed to minimize the possibility of inaccurate results due to low sample volume. The accuracy of the glucose test strip was demonstrated by comparing 393 capillary blood glucose obtained by YSI Glucose analyzer (YSI Inc.,

Yellow Springs, OH). Agreement between the two methods of measurements was observed with a correlation coefficient (r)> 0.98, mean absolute bias of 4.9% and a 3.5% reproducibility of normal glucose concentration. Capillary blood samples were measured with three test strips in three SMBG devices and average of the three readings was used.

Statistical analysis

Incremental AUCs for each test meal were calculated and the data were expressed as mean±SE. Two-way ANOVA were used to test the main effect and the interaction between age and test meal. Mean contrasts according to modified Bonferroni inequalities were used to analyzed significance. Mean values of the four test meals in each age group were compared by analysis of variance (ANOVA). The Tukey's multiple comparisons test of means was used to compare treatments pairwise. Simple correlations were determined by Pearson's correlation coefficient (r). Partial correlations were measured between postprandial glycemic response (AUC) and age, BMI and dietary fat ratios by controlling for the impact of energy intake. Analysis of the data was carried out with SPSS version 11.5 J statistical software. P value less than 0.05 were considered statistically significant.

C．研究結果

Originally there were 10 subjects in each age group; however, one subject of the forties was dropped from the study due to physical problem. Characteristics of the study subjects were shown in Table 2. The heights, weights, BMIs and fasting blood glucose showed no significant difference among the three age groups (p>0.05). A main effect of age and age-by-test meal interactions were significant (both p<0.01; Figure 1). In the subjects of the twenties, glycemic response of meal A was higher than that of the others after 60 min, although the difference was not significant (Figure 1a). The AUCs of meal A, B, C and D were 56±7, 51±6, 43±6 and 40±7 mg/dl/h, respectively, with no significant difference among each other.

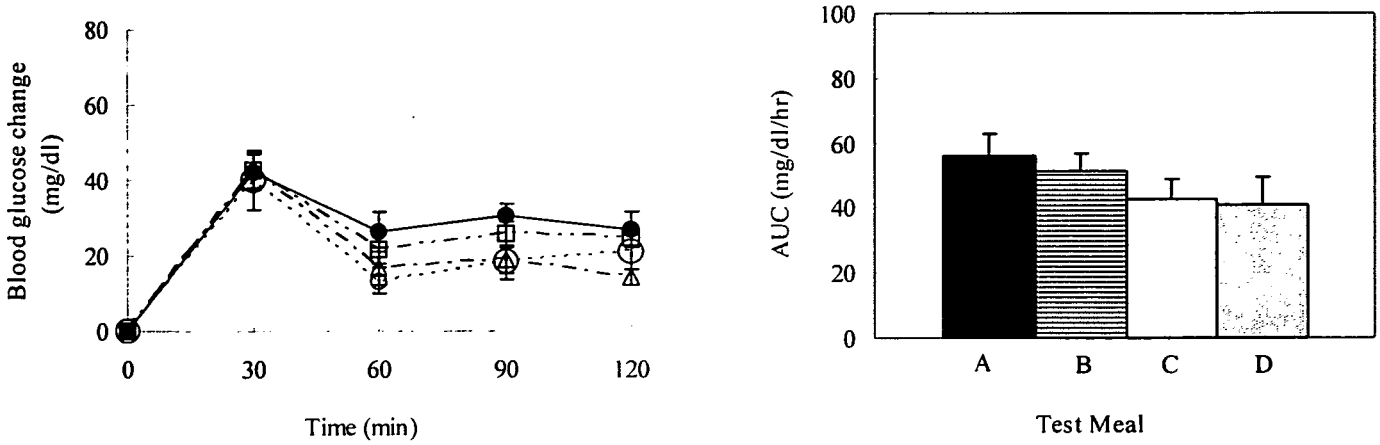
In the subjects of the forties, meal A which contained vegetables had significantly lowered glycemic response in postprandial 30 min when compared with meal C (p<0.05, Figure 1b). The AUCs of meal A, B, C and D were 48±6, 41±4, 70±7 and 55±7 mg/dl/h, respectively. Meals A and C tended to show different glycemic response for the 2 h (p=0.07).

Table 2.Characteristics of the study subjects

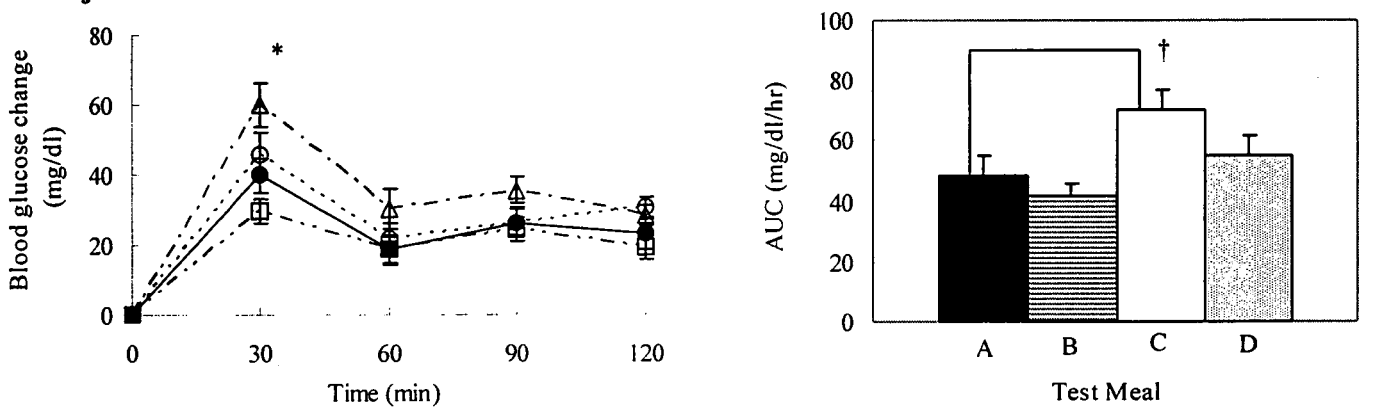
Group	Age (y)	Height (cm)	Weight (kg)	BMI (kg/m^2)	Fasting Blood Glucose(mg/dl)
Twenties (n=10)	23.4 ± 0.5	155.1 ± 1.2	44.0 ± 2.3	18.2 ± 0.8	85.0 ± 2.8
Forties (n=9)	42.3 ± 0.6	153.5 ± 1.6	46.1 ± 2.2	19.5 ± 0.6	88.3 ± 2.3
Sixties (n=10)	61.4 ± 0.4	153.2 ± 1.1	47.6 ± 1.7	20.3 ± 0.8	92.6 ± 1.3

Data were presented as means ± SE.

a. Subjects of Twenties



b. Subjects of Forties



c. Subjects of Sixties

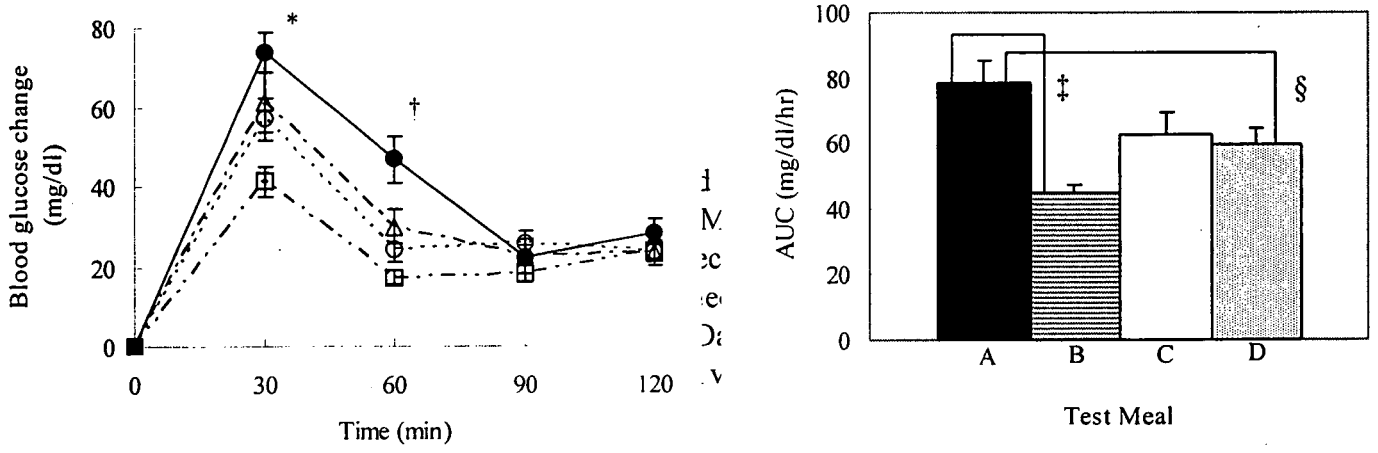


Figure 1. Postprandial blood glucose level and the AUC after subjects consumed four test meals (●, A; □, B; Δ, C and ○, D) for 120 min. Meal A was compared with the other three test meals. Two-way ANOVA showed a main effect of age and a significant age-by-test meal interaction (both $p<0.01$). (a) Data for subjects of twenties. (b) Data for subjects of forties. $^{*}p<0.05$, and $^{\dagger}p=0.07$ for A vs. C. (c) Data for subjects of sixties. $^{*}p<0.01$ A vs. B. $^{\dagger}p<0.001$ A vs. B, $p<0.05$ A vs. C, and $p<0.01$ A vs. D. $^{\ddagger}p<0.001$, $^{\S}p=0.07$.

In the subjects of sixties, more carbohydrate contained in meal A showed a considerable effect on glycemic response which was significantly higher than meal B in the postprandial 30 min ($p<0.01$) and 60 min ($p<0.001$) (Figure 1c). In the postprandial 60 min, meal A had a significant converse effect on glycemic response compared with meal C ($p<0.05$). Glycemic response of meal D was significantly lower than that of meal A in the postprandial 60 min ($p<0.01$). The AUCs of meals A, B, C and D were 79±6, 45±3, 63±6 and 59±5 mg/dl/h, respectively. The glycemic response for 2 h was significantly different between meals A and B ($p<0.001$), and it tended to show significance between meals A and D ($p=0.07$).

When comparing the glycemic responses of the same test meal among three age groups (Figure 2), significant differences in meal A was observed for those in the forties versus the sixties ($p<0.01$) and in meal C for the subjects in the twenties compared to the forties ($p<0.05$). Pearson's correlation analyses indicated age was significantly correlated with postprandial glycemic response (AUC) ($r=0.26$, $p<0.01$) (Table 3). A significant negative correlation was observed between AUC and dietary fat ratio ($r=-0.28$, $p<0.01$). There was no association between BMI and AUC ($r=-0.12$, $p=0.20$). After partial correlation analysis, the correlations between AUC vs. age and AUC vs. dietary fat ratio remained significant (beta=0.26, $p<0.01$ and beta=-0.27, $p<0.01$, respectively).

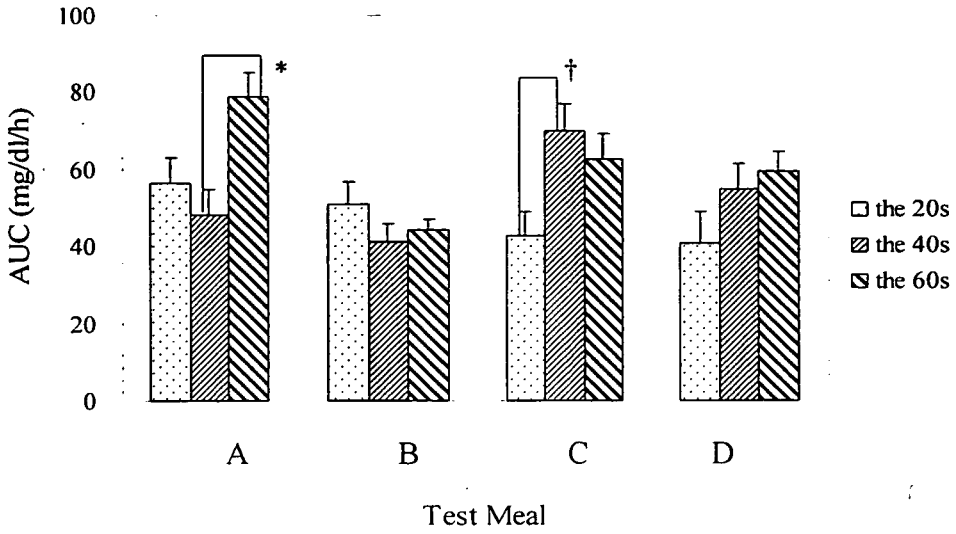


Figure 2. Postprandial glycemic responses (AUCs) of the same test meals when compared among the three age groups. $^{*}p<0.01$, $^{\dagger}p<0.05$.

Table 3. Correlation analyses between postprandial glycemic response (AUC) and age, BMI and dietary fat ratio.

	Postprandial glycemic response (AUC)			
	r *	*p*-value	beta*	*p*-value
Age	0.26	<0.01†	0.26	<0.01†
BMI	-0.12	0.20	-0.12	0.20
Dietary fat ratio	-0.28	<0.01†	-0.27	<0.01†

* *r* for Pearson's correlation coefficient, and beta for partial correlation coefficient
† $p<0.01$ significant difference

D. 考察

The diet with about 70% energy from carbohydrate which is commonly consumed by Vietnamese increased glycemic response, especially in the elderly people. The increased glycemic response was considered to be mainly due to a low dietary fat ratio and excess carbohydrate since protein intake levels were similar being 13-15% of total energy intake. The additional amount of fat in meal D reduced glycemic response when compared with meal A, despite identical amount of carbohydrate. Furthermore, the glycemic response of meal A displayed marked postprandial hyperglycemia compared with meal B. Our results were consistent with other studies which pointed out that fat contained in a mixed meal would delay the absorption of carbohydrate and attenuate the glycemic response (*11, 12*). Though fat was thought as none GI (*8*) to attenuate the glycemic response; however, its high energy density could not be ignored.

Glycemic response of meal A displayed marked postprandial hyperglycemia in the subjects of sixties compared with meal B, while the same effects couldn't be observed in the subjects of twenties and forties. It may be speculated that the little difference in the AUC observed in the subjects of twenties and forties might be due to the leveling off in glycemia as indicated by Brand-Miller et al. (*24*). In their study involving lean healthy volunteers, Brand-Miller et al. (*24*) pointed out that increasing the glycemic load produced a stepwise increase in glucose AUC only observed at the low doses. In that study, five doses (one, two, three, four and six slices) of bread were tested. The dose-response relationships observed at lower doses and a leveling off in glycemia after a load of four slices of bread suggests healthy individuals are able to control glycemia within narrow physiological boundaries by increasing the amount of insulin secreted (*24*). On the other hand, test meals in the present study were designed to be close to the daily intake in Vietnam. After converting amount of rice into carbohydrate, 84 g and 66 g of carbohydrate were contained in meal A and B, respectively. These amounts had been over 52 g carbohydrate which was equivalent to the mentioned four slices of bread. The glycemic effect caused by different amount of carbohydrate seemed to be attenuated by other factors such as fat and protein contained in side dishes (*11*). However, the considerable difference observed in the subjects of the sixties might be caused by age or potentially by adipose tissue (*25, 26*). It has been indicated that abdominal fat and body fat percentage are increasing in Vietnamese, especially in females (*27*). It is also worth mentioning that decreasing insulin sensitivity due to body fat increased with age has been observed (*26*). However, it was the limitation of this study that only blood glucose used as an indicator and BMI used as anthropometric criteria were inadequate to provide a further explanation.

Studies indicated that dietary fibers contained in vegetables delayed the absorption of carbohydrates and ameliorated the postprandial glycemic response (*17-20*). In this study we observed interesting phenomenon. The favorable effect was only in the forties but not in the twenties and sixties. The results of twenties and forties were also different. In the twenties, AUC of meals A and C were similar and low but in the sixties, AUC of both test meals were similarly high. The results may suggest that the young group had the ability to control blood glucose level regardless of the dietary vegetable. In the elderly group, AUC was high even though they took the meal with vegetable (meal A). Nevertheless, an increase in the AUC was not observed by taking the meal without vegetable (meal C). This observation needs further studies to

elucidate the favorable effects of dietary vegetable in the elderly.

The GI might be of some help to patients with impaired glucose tolerance (*11, 12*). Nevertheless, the GI concept, especially considering its interpretation by health professionals or the general population, should not be the only, nor the most important, criterion to judge a food (*12*). A low dietary fat ratio and excess carbohydrate could also account for increase glycemic response, not only using rice as a staple food. Our observations was in line with the recommendation by the ADA which states that the amount of available carbohydrate is more important than the source (*28*), since most of the time individuals consume a mixed meal rather than a single food. Dietary guideline is needed to base on ordinary dietary habit, or it will make futile. The dietary pattern of consuming rice as a staple food with other side dishes might represent a good dietary habit of Asians with total energy intake being taken into account. However, such test meals are probably not exactly representative of those in everyday life, further studies involving large number of young and elderly healthy subjects are needed to elucidate the effect of dietary FC ratio in mixed meals.

In conclusion, the present study showed that postprandial glycemic responses were different among three age groups, despite the consumption of the same test meal. The diet with about 70% energy from carbohydrate which is commonly consumed by Vietnamese increased glycemic response, especially in the elderly people. Dietary vegetable may also be beneficial to prevent such an increase in glycemic response.

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E.結論

以上の結果、ベトナム人が通常摂取する食事は糖質が高く、特に高齢者の食後血糖値を上昇すること、および野菜は食後血糖値の上昇を抑制することが示唆された。

平成１９年度厚生労働科学研究費補助金（社会保障国際協力推進研究事業）
分担研究報告書

HDL を介した動脈硬化防御機構における脂肪細胞由来分子 Adiponectin の役割

分担研究者（大阪大学大学院医学系研究科 循環器内科学 山下 静也）

研究要旨

我々は脂肪細胞特異的な分泌蛋白として同定した Adiponectin（APN）が様々な抗動脈硬化作用を有することをこれまでに報告してきた。また、これまでに行った疫学的検討で、血清 APN 値と HDL-C 値が正の相関を示すこと、内臓脂肪面積と逆相関すること、および虚血性心疾患発症者、肥満者、２型糖尿病患者で血中 APN 値が低下することも報告している。これらの事実の蓄積を考え合わせると、APN は動脈硬化防御機構であるコレステロール逆転送系に対し、これを賦活化する可能性があると推測されるが、かかる観点からの報告は未だない。本研究ではｉ）APN が肝における HDL 新生の必須因子である ATP-binding cassette transporter-A1, G1(ABCA1、ABCG1)やアポ蛋白 A-1 分泌に与える作用、およびii）末梢組織で ABCA1、ABCG1 を介して行われるアポ蛋白(apo)A-I や HDL によるコレステロール引き抜き(cholesterol efflux：CE）に APN が与える作用を検討した。APN は肝癌由来細胞株 HepG2 細胞において、アポ蛋白 A-1 の mRNA を APN 濃度依存性に増加し、30 μg/ml APN では ApoA-1 の培養液中への分泌亢進が認められ、ABCA1 の mRNA 発現量も APN 濃度依存性に増加させた。ヒト単球由来マクロファージでは、10 μg/ml APN は ABCA1, ABCG1 の mRNA 発現量を、それぞれ 2.3 倍、2.2 倍に増加させた。ApoA-1 を介したコレステロール引き抜きは、10μg/ml APN の添加で、8.1 倍に増加した。以上のデータから、APN は肝臓における HDL 新生と末梢細胞における CE の亢進を介して、HDL-C を増加させ、コレステロール逆転送系を活性化させることが明らかになった。

A. 研究目的

我々の研究室で脂肪細胞特異的な分泌蛋白として同定した Adiponectin は、内皮細胞の接着分子発現の抑制、マクロファージの泡沫化の抑制、血管平滑筋細胞の増殖抑制、インスリン感受性の改善などの抗動脈硬化作用を有することを我々は報告してきた。また、これまでの疫学的検討で、我々は血清 APN 値と HDL-C 値が正の相関を示すこと、内臓脂肪面積と逆相関すること、および虚血性心疾患発症者、肥満者、２型糖尿病患者で血中 Adiponectin 値が低下することを報告した。これらの事実の蓄積を考え合わせると、Adiponectin はコレステロール逆転送系に対し、これを賦活化する可能性があると推測されるが、いまだ世界において検討された報告はなかった。そこで我々は、ｉ）Adiponectin が肝における HDL 新生に必須である因子 ATP-binding cassette transporter- A1、G1(ABCA1、ABCG1)や ApoA-1 の分泌に与える作用、お

よびii)Adiponectinが末梢組織でABCA1、ABCG1を介して行われるリポ蛋白によるコレステロール引き抜き（cholesterol efflux：CE）に与える作用を明らかにすることを目的とした。

B. 研究方法

1）Recombinant Adiponectinを細胞培養液中に添加し、HepG2細胞のApoA-1, ABCA1、ABCG1、SR-BIの発現量への影響について検討する。さらに、HepG2細胞からのApoA-1およびApoB-100分泌に対するAdiponectinの作用について検討する。

2）Adiponectin KOマウス の血漿脂質解析、肝臓におけるApoA-I、ABCA1、ABCG1の発現量の検討する。

3）ヒト単球由来マクロファージからのコレステロールくみ出し機構(CE)に対するAdiponectinの影響を検討する。

(倫理面への配慮)

本研究は大阪大学動物実験委員会の承認を受けている。

C. 研究結果

1) AdiponectinのHepG2培養液中添加により、ApoA-I分泌は増加したが、VLDLの構成アポ蛋白であるApoB100分泌は低下していた。また、ApoA-I、ABCA1発現量は有意に増加していたが、ABCG1、SR-BI発現量には差は認められなかった。

2).In vivoでの検討として、Adiponectin-KO miceをWild typeと比較検討すると、血清TC、PL濃度に差は見られなかったが、TG濃度は有意に増加していた。血清中のApoA-I濃度はAdiponectin-KOマウスにおいて減少しており、ApoB100濃度は増加した。また、肝臓でのApoA-IおよびABCA1の発現量は有意に低下していた。

3) ヒト単球マクロファージの細胞培養液中へのAdiponectin添加では、ABCA1の発現量は濃度依存的に増加した。ApoA-Iを介した細胞内からのコレステロールのくみ出しは有意に増加した。

D. 結論および考察

これらの結果を総括すると、Adiponectinは肝臓におけるApoA-1及びABCA1の転写を促進し、ApoA-1は分泌、ABCA1は細胞膜上への発現を増大するものと考えられ、ここからHDLの新生が促進されると考えられた。また、AdiponectinはABCA1の発現誘導を介してマクロファージにおけるCEを促進することも明らかになった。このように、Adiponectinが肝臓におけるHDL産生と末梢細胞におけるCEに関わる種々の因子に関与することは、Adiponectinによる動脈硬化抑制作用の一翼を担っているものと考えられる。内臓脂肪蓄積時に認められるAdiponectinの低下は、肝臓におけるHDL新生や、マクロファージにおけるCEの低下を介してHDL-Cを低下させ、さらに動脈硬化防御機構であるコレステロール逆転送系の抑制を介して動脈硬化の進行に繋がる可能性が示された。

E. 健康危険情報

特になし

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H. 知的財産権の出願、登録状況

なし

平成１９年度厚生労働科学研究費補助金（社会保障国際協力推進研究事業）
分担研究報告書

日本人糖尿病患者におけるハイリスク高脂血症 IIa 型の解析

分担研究者　（筑波大学　島野　仁）

研究要旨　IIa 型高脂血症の臨床的特徴について検討するために、筑波大学糖尿病外来の通院患者について IIa 型（TC>220　mg/dL あるいは LDLC>160 mg/dL かつ　TG<150 mg/dL）高脂血症を調査した。さらに高脂血症がより重症なグループ（TC>260 mg/dL あるいは LDLC＞200mg/dL かつ　TG<150 mg/dL）をハイリスク IIa 型として通常 IIa 群と比較した。　その結果、糖尿病患者において高脂血症 IIa 型の特徴としては、頻度は女性の方が男性よりも多く、重症 IIa 型は通常型よりも年齢が若いことがわかった。治療薬としてほとんどがスタチンを使用されていた。女性の方は、通常，重症型とも管理良好目標達成しており、ハイリスクの方がむしろコレステロールの低下が大きい必ずしもストロングを使用しておらずレギュラーでも管理可能であった。一方、男性は，通常，重症型ともコレステロール低下が同じで重症型では管理不十分であった。　IIa 型についてスタチンは TG，HDL の改善に寄与していなかった。
これらをふまえ、　スタチン中心の治療が図られており、　女性は概ね管理良好である一方、結論として、LDL コレステロールがより高値の重症型の男性については管理が不十分で、　ハイリスクグループには、今後エゼチミブ、コレスチミドなど他剤との併用を考慮すべきと考えられた。

A. 研究目的

IIa 型高脂血症は、最も確立した動脈硬化の強力なリスクである高 LDL コレステロール血症を特徴とする。　その成因は、腎疾患・内分泌疾患等に続発して起こる場合や、二次性要因のない原発性に分類される。 血中 LDL コレステロールは　LDL 受容体により、血中から除去されるため、LDL 受容体活性が、そのレベルを規定し、また最も汎用されているスタチンの作用機序も LDL 受容体の活性化にある。原発性高脂血症としては、特にもっとも多い遺伝性疾患と考えられる家族性高コレステロール血症（FH, LDL 受容体欠損症）が含まれ、これは難治性原発性高脂血症の最も重要な対象疾患である。　特に本研究でサブ分類する重症型 IIa には、この FH が多く含まれていると考えられる。今後の脂質異常症の診療指針上、動脈硬化症のハイリスク群として、重症型 IIa と通常型 IIa の比較研究が重要と考え、当院の外来患者における IIa 型高脂血症の頻度と臨床像について検討した。

B. 研究方法

外来患者：当院内分泌代謝糖尿病内科 10 名の担当医に初診以来通常 1－ 3 ケ月の間隔で定期的に検査，治療通院している患者 1416 名について、IIa 型高脂血症以下 IIa 型を抽出した。　スクリーニングの方法は、血中脂質値が下記の条件を通院中の検査で一度でも満たした症例を、IIa 型高脂血症（以下 IIa 型）として解析した。血清 TC(LDLC)値 220 (140)mg/dl 以上かつ血清 TG 値 150mg/dl 未満（正常）を満たした症例を通常 IIa 型高脂血症、血清 TC(LDLC)値 280 (200) mg/dl 以上かつ血清 TG 値 150 mg/dl 未満を満たした症例を重症型 IIa 型高脂血症として抽出した。　特に当科通院患者は

主として糖尿病であり，約７０％をしめる事は特記すべき点である。

解析に用いたIIa型高脂血症

通常IIa

TC＞220mg/dl あるいはLDLC>140mg/dl

および　TG＜150mg/dl

重症IIa

TC＞280mg/dl あるいはLDLC>200mg/dl

および　TG＜150mg/dl

スクリーニング時の検査値を治療前値とし，以後生活習慣の改善，薬物治療を開始し，直近の外来受診時の検査値を治療後値とした。

該当患者を男女別に、年齢，身長，体重，BMI、ウエスト周囲径，収縮期血圧，拡張期血圧，HbA1c，治療前後の総コレステロール，トリグリセリド値，HDLコレステロール値，LDLコレステロール（計算値 TC － HDLc － TG/5），nonHDLコレステロール（TC － HDLc），背景因子として糖尿病，高血圧，メタボリックシンドローム，虚血性心疾患，脳梗塞の有無，動脈硬化症診療ガイドライン（2007年度版）に従ったカテゴリー2次予防（CHDあり）、１次予防カテゴリーI, II, III の分類，治療内容（食事運動療法，薬物スタチン，フィブラート，レジン，プロブコール，ニコチン酸、エセチミブ）について調べた。

これらについて、上記通常IIa，重症型IIa間で比較，検討した。

C. 研究結果およびD. 考察

1. 通常IIaグループの特徴

1400名の外来患者中91名（６．５％）がIIa型高脂血症を呈した。　７０％が糖尿病であり、糖尿病患者におけるIIa型合併率は、２０％を超える本邦の報告と比較すると極めて低い頻度であった。　これは、高脂血症よりも糖尿病の診断が先行しており、　既に食事療法などが開始していることの影響が考えられる。　一方前年度解析したTC，TGともに高値を示すIIb型は１５％前後で、従来の報告に近かった。　IIa９１名中、男性は27名、女性は６４名と男性が少なく、倍近い差があった。　IIb型は男女ともほぼ同数であったが、男性に高トリグリセリド血症が多いことと関連していると考えられる。　またBMIは男女とも２２－２３、血圧１２０台と正常であった。　肥満傾向を示したIIbとは好対照であった。　糖尿病患者が7割を占めるがHbA1cは6.6前後の比較的良好な血糖コントロールであった。

２．重症IIa群の特徴

重症IIa群と通常IIa群を比較した。　男女とも重症IIa群の方が年齢が顕著（１４歳）に若かった。　それと関連して、特に女性で、BMI，ウエスト、収縮期血圧が低い傾向にあった。　男では肥満度、血圧に差はなかった。　HbA1cは男女とも差がなかったが、７％台であったIIb型に比して血糖のコントロールは良好であった。

治療前の血中脂質データ　（表）

グループ分けの指標となっているTCならびにLDLCは、重症IIa群は通常IIa群に比べ男性の場合３０－３５mg／dl高かった。しかし年齢が若いこと関連してかTGは低く、HDLは高かった。　女性も同様に、重症IIa群は通常IIa群に比べ、TCが４０mg/dl 高いが、TGが２０mg/dl 低く、LDLCは４５mg/dl 高い傾向があった。

治療後の血中脂質データ　（表1）

治療内容は、通常IIa群では男の９０％、女の６０％が、重症IIa群では男女の８０％がスタチンを利用していた。　しかしスタチンのうちストロングスタチンの使用が多いが、レギュラースタチンも３、４割使用され、重症度とは関連がなかった。

治療による効果は表の通りである。男の通常群、