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＜特集：国際会議＆サテライト・シンポジウム 要旨集＞

第5回「栄養とエイジング」国際会議
ヘルシーエイジングを目指して～
ライフステージ別栄養の諸問題
2007年10月31日、11月1日
於：国際連合大学ウ・タント国際会議場

サテライト・シンポジウム
「食品成分・素材の安全性の考え方」
2007年11月2日
於：国際連合大学ウ・タント国際会議場

目　次

ILSI
International Life Sciences INSTITUTE
特定非営利活動法人
国際生命科学研究機構
International Life Sciences Institute of Japan

International Life Sciences Institute, ILSI は、1978年にアメリカで設立された非営利の団体です。

ILSIは、健康・栄養・安全性・環境に関わる問題の解決および正しい理解を目指すとともに、今後発生する恐れのある問題を事前に予測して対応していくなど、活発な活動を行っています。現在、世界中の400社以上の企業が会員となって、その活動を支えています。

多くの人々にとって重大な関心事であるこれらの問題の解決には、しっかりとした科学的アプローチが不可欠です。ILSIはこれらに関連する科学研究を行い、あるいは支援し、その成果を会合や出版物を通じて公表し、啓蒙に役立てています。その活動の内容は世界の各方面から高く評価されています。

また、ILSIは、非政府機関(NGO)の一つとして、世界保健機関(WHO)とも密接な関係にあり、国連食糧農業機関(FAO)に対しては特別アドバイザーの立場にあります。アメリカ、ヨーロッパをはじめ各国で、国際協調を目指した政策を決定する際には、科学的データの提供者としても国際的に高い信頼を得ています。

特定非営利活動法人国際生命科学研究機構(ILSI Japan)は、ILSIの日本支部として1981年に設立されました。ILSIの一員として世界的な活動の一翼を担うとともに、日本独自の問題にも積極的に取り組んでいます。

第5回「栄養とエイジング」国際会議
ヘルシーエイジングを目指して～ライフステージ別栄養の諸問題

2007年10月31日、11月1日
国際連合大学 ウ·タント国際会議場（東京・青山）

主　催：International Life Sciences Institute（ILSI）
特定非営利活動法人 国際生命科学研究機構（ILSI Japan）

共　催：ILSI北米支部（ILSI North America）
ILSIヨーロッパ支部（ILSI Europe）
ILSI中国事務所（ILSI Focal Point in China）
ILSI東南アジア支部（ILSI SEA）
国際アミノ酸科学協会（ICAAS）

後　援：厚生労働省
農林水産省
東京都
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日本基礎老化学会
日本臨床栄養学会
社団法人 日本栄養·食糧学会
社団法人 日本栄養士会
日本応用老年学会

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サテライト·シンポジウム「食品成分·素材の安全性の考え方」

2007年11月2日
国際連合大学 ウ·タント国際会議場（東京・青山）

主　催：特定非営利活動法人 国際生命科学研究機構（ILSI Japan）
国際アミノ酸科学協会（ICAAS）

第5回「栄養とエイジング」国際会議／サテライト・シンポジウム開催にあたって

特定非営利活動法人 国際生命科学研究機構
理事長　　木村　修一

ILSI Japan主催の「栄養とエイジング」国際会議も5回を迎えることになりました。第1回は、初代会長である小原哲二郎先生の発案で、1991年にILSI Japanの創立10周年を記念して行われたものでした。そして第2回は、日本が世界一の長寿国なので日本でやるのがふさわしいとの本部の強い推薦もあり、再度、日本で開催となりました。その後、第3回、第4回と4年毎に行われることを通して、日本が開催国となるということが定着した感があります。いずれの回においても、時代の求める栄養学的問題は何かをディスカッションして加齢に関する栄養学のトピックスを選んで国内外の研究者の集いを催して参りました。

今回は、ライフステージ別栄養の諸問題に焦点を絞り、「ヘルシーエイジングを目指して～ライフステージ別栄養の諸問題」という副題で、それにふさわしい3つのセッションを設けました。その第一は「ライフステージ特有の栄養と生活習慣病リスク」、第二は「胎児期栄養と生活習慣病リスク」、そして第三は「高齢者のQOL維持を目的とした栄養の役割」としました。さらにサテライト·シンポジウムとして、「食品成分・素材の安全性の考え方」についてディスカッションを行うことになりました。

いまや肥満の増加は世界の趨勢であり、日本においても、特に男性に見られるように、年を追う毎に増え続けていますが、不思議なことに日本の女性の場合、肥満が減り、るいそう（痩せ過ぎ）が増えているのです。若い女性の間ではダイエットが大はやりです。このところ、日本におけるメタボリック・シンドロームの診断基準が決まり、日本人特有の遺伝要因により糖尿病への罹患率の上昇に大きな関心が集まっており、内臓脂肪蓄積型の肥満がメタボリック·シンドローム発症の重要な要因と目されています。

一方、低出生体重児が大人になってからのメタボリック·シンドローム発症のリスクの高いことが疫学調査から明らかになってきていることを考えると、妊娠期のダイエットはメタボリック·シンドロームのリスクを高める可能性が大いにあると考えられます。最近における日本での低出生体重児の割合の上昇は、日本の女性の痩せ過ぎの増加と無関係ではないと考えられるからです。男性の肥満と同様に女性の痩せ過ぎもまたメタボリック·シンドロームのリスクとして考慮すべきであると思うのです。

本会議では、このような視点でのディスカッションも期待されると思います。

また、この数年、日本では、食品の安全の問題が大きく社会的問題としてクローズアップされました。サテライト·シンポジウムを企画したのもこのような社会的背景もあるからです。この第5回「栄養とエイジング」国際会議に是非おいで下さるようお誘い申し上げます。

The 5th International Conference on Nutrition and Aging and Its Satellite Symposium

OPENING REMARKS

Shuichi Kimura, Ph.D.
President, ILSI Japan

This will be the fifth International Conference on "Nutrition and Aging" sponsored by ILSI Japan. The first meeting was held in 1991 in celebration of the tenth anniversary of ILSI Japan, at the suggestion of Tetsujiro Obara, ILSI Japan's first president. And the second one was held also in Japan at the ILSI headquarters' strong request that it be held in Japan because Japanese people have the world's longest life spans. As the meeting has been held in Japan every four years, it feels like Japan's hosting the meeting has been regularized. In each of the past meetings, we discussed what nutritional issues meet the needs of the times and chose a proper nutritional topic related to aging for researchers from home and abroad after

This time, we focused on several nutritional problems according to life stage, and planned three sessions based on them with the subtitle "Nutrition Problems by Life Stages." The first one is "Risk of Life-style Related Diseases and Characteristic Nutrition by Life Stage," the second one, "Fetal Nutrition and Risk of Life-style Rrelated Diseases," and the third, "The Role of Exercise and Nutrition Maintenance of QOL in People of Advanced Age." In addition, we decided to hold a satellite symposium to discuss "Considerations for Setting Upper Intake Levels for Nutrition."

Nowadays there is an increasing number of obese people worldwide. In Japan as well, obesity rates are increasing yearly especially in men. In contrast, curiously enough, obese women are decreasing in number and overly-thin women are increasing. There is a diet craze among Japanese young women. It may be one of the reasons for those phenomena. Recently a diagnostic criterion for the so-called metabolic syndrome in Japan has been determined. There has been a lot of attention given to the increased rate of diabetes caused by the inheritable factors unique to Japanese people, and obesity caused by the accumulation of visceral fat is believed to be a significant factor for metabolic syndrome development.

Meanwhile, considering that epidemiologic studies have demonstrated that low-birth-weight infants have a higher risk of developing metabolic syndrome when they grow up, it seems more likely that dieting during pregnancy significantly increases the risk of metabolic syndrome. A recent increase in the percentage of low-birth-weight infants in Japan does not seem to be unconnected with the growing number of overly-thin Japanese women. I think that females being extremely underweight should be considered a risk of metabolic syndrome as well as male obesity.

I hope that discussions from a perspective like this will be conducted.

Recently in Japan, food safety has become a major concern to the people as one of the major social problems. Such a social background is part of the reason that the satellite symposium was organized. I hope you will be able to join us in the fifth International Conference on "Nutrition and Aging."

組　織

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	Yoshiko Yamazaki	Food Science Information Center
	Hiroshi Watanabe	Nestlé Japan Ltd.

●Administration

Atsuko Niimura

ILSI Japan Secretariat

日程表

	【第5回「栄養とエイジング」国際会議】		【サテライト・シンポ】
	★10月31日（水）	★11月1日（木）	★11月2日（金）
9:00	9:00- 受付・登録	9:00- 受付・登録	9:00- 受付・登録
	9:30-9:40 開会の挨拶	9:30-12:30 セッションⅡ 胎児期栄養と生活習慣病リスク	9:30-12:45 午前の部
10:00	9:40-12:30 セッションⅠ ライフステージ特有の栄養と 生活習慣病リスク		
11:00			
12:00			
	12:30-14:00 昼食＆ポスターセッション	12:30-14:00 昼食＆ポスターセッション	12:45-13:50 昼食
13:00			
14:00	14:00-17:20 セッションⅠ（続き） ライフステージ特有の栄養と 生活習慣病リスク	14:00-17:20 セッションⅢ 高齢者のQOL維持を目的とした 栄養の役割	13:50-17:25 午後の部
15:00			
16:00			
17:00		17:20-17:30 閉会の挨拶	
18:00	18:00- レセプション		
19:00			

CONFERENCE AT A GLANCE

	【Nutrition & Aging Conference】		【Satellite Symposium】
	★31, October	★1, November	★2, November
9:00	9:00- REGISTRATION	9:00- REGISTRATION	9:00- REGISTRATION
	9:30-9:40 OPENING REMARKS	9:30-12:30 SESSION Ⅱ Fetal Nutrition and Risk of Life-style Related Diseases	9:30-12:45 A.M. SESSION
10:00	9:40-12:30 SESSION Ⅰ Risk of Life-style Related Diseases and Characteristic Nutrition by Life Stage		
11:00			
12:00			
	12:30-14:00 Lunch and Poster Session	12:30-14:00 Lunch and Poster Session	12:45-13:50 Lunch
13:00			
			13:50-17:25 P.M. SESSION
14:00	14:00-17:20 SESSION Ⅰ (continued) Risk of Life-style Related Diseases and Characteristic	14:00-17:20 SESSION Ⅲ The Role of Exercise and Nutrition Maintenance of	
15:00	Nutrition by Life Stage	QOL in People of Advanced Age	
16:00			
17:00		17:20-17:30 CLOSING REMARKS	
18:00	18:00- Dinner / Reception		
19:00			

プログラム

【第5回「栄養とエイジング」国際会議】

★10月31日（水）

9:00- 受付・登録

9:30-9:40 **開会の挨拶**

木村修一（ILSI Japan）

セッションⅠ　ライフステージ特有の栄養と生活習慣病リスク

座長　木村修一

9:40-10:20 **【基調講演】**
「肥満と生活習慣病、食品産業の役割」
渡邊 昌（独立行政法人 国立健康・栄養研究所）

10:20-11:00 **「メタボリックシンドロームの分子機構と治療戦略」**
門脇 孝（東京大学大学院医学系研究科）

11:00-11:40 **「テーラーメイド栄養学」**
坂根直樹（独立行政法人 国立病院機構京都医療センター臨床研究センター）

11:40-12:20 **「動脈硬化性疾患の一次予防―メタボリックシンドロームを含めて―」**
中村治雄（三越厚生事業団）

12:20-12:30 質疑応答

12:30-14:00 昼食＆ポスターセッション

座長　渡邊 昌

14:00-14:40 **「小児のメタボリックシンドロームとその診断基準」**
大関武彦（浜松医科大学）

14:40-15:20 **「歯周病と体の健康に関連した研究の概要」**
デニス・F・キニン（米国・ルイビル大学）

15:20-15:30 質疑応答

15:30-15:50 休憩

15:50-16:30 **「ペプチドによる神経性の摂食調節機構」**
中里雅光（宮崎大学医学部内科学講座）

16:30-17:10 **「機能性食品とエネルギーの消費」**
マルガリート・S・ウェスタープ（オランダ・マーストリヒト大学）

17:10-17:20 質疑応答

18:00- レセプション

PROGRAM

【The 5th International Conference on "Nutrition and Aging"】

★Wednesday, October 31

9:00-	REGISTRATION
9:30-9:40	**OPENING REMARKS**
	Dr. Shuichi Kimura, ILSI Japan

SESSION I　Risk of Life-style Related Diseases and Characteristic Nutrition by Life Stage

Chair: Dr. Shuichi Kimura

9:40-10:20	**【KEYNOTE LECTURE】**
	Obesity and Life-style Related Diseases in Japan: Roles of Food Industry
	Dr. Shaw Watanabe, National Institute of Health and Nutrition
10:20-11:00	**Metabolic Syndrome: Pathophysiology and Treatment Strategy**
	Dr. Takashi Kadowaki,
	Graduate School of Medicine, The University of Tokyo
11:00-11:40	**Tailor-made Nutrition**
	Dr. Naoaki Sakane, National Hospital Organization Kyoto Medical Center
11:40-12:20	**Primary Prevention of Artherosclerotic Vascular Diseases in Japan with Special Reference to Metabolic Syndrome**
	Dr. Haruo Nakamura, Mitsukoshi Health and Welfare Foundation
12:20-12:30	Q & A
12:30-14:00	Lunch and Poster Session

Chair: Dr. Shaw Watanabe

14:00-14:40	**Metabolic Syndrome and Its Diagnostic Criteria for Japanese Children and Adolescents**
	Dr. Takehiko Ohzeki, Hamamatsu University School of Medicine
14:40-15:20	**Overviews of the Links between Periodental Disease and Systemic Health**
	Dr. Denis F. Kinane, University of Louisville, School of Dentistry, USA
15:20-15:30	Q & A
15:30-15:50	Coffee Break
15:50-16:30	**Neuronal Mechanisms of Feeding Regulation by Peptides**
	Dr. Masamitsu Nakazato,
	Division of Internal Medicine, Miyazaki Medical College, University of Miyazaki
16:30-17:10	**Functional Food and Energy Expenditure**
	Dr. Margriet S. Westerterp-Platenga, Maastricht University, The Netherland
17:10-17:20	Q & A
18:00-	Dinner / Reception

★11月1日（木）

9:00-　受付・登録

セッションⅡ　胎児期栄養と生活習慣病リスク

座長　木村修一

9:30-10:10　**【基調講演】**
「小児期における生活習慣病予防」
坂本元子（和洋女子大学）

座長　坂本元子

10:10-10:50　**「妊娠期の低栄養の現状」**
瀧本秀美（国立保健医療科学院）

10:50-10:55　質疑応答

10:55-11:00　休憩

11:00-11:40　**「胎生期の栄養環境と成長後における肥満発症」**
伊東宏晃（独立行政法人 国立病院機構大阪医療センター）

11:40-12:20　**「胎児期を含めた、生活習慣病に関する栄養プログラミング」**
キャロライン･マクミレン（オーストラリア・サウス･オーストラリア大学）

12:20-12:30　質疑応答

12:30-14:00　昼食＆ポスターセッション

セッションⅢ　高齢者のQOL維持を目的とした栄養の役割

座長　小林修平（人間総合科学大学）

14:00-14:40　**「高齢者の食事と生活習慣病」**
佐々木 敏（東京大学大学院、独立行政法人 国立健康･栄養研究所）

14:40-15:20　**「慢性閉塞性肺疾患（COPD）患者における栄養療法と運動療法の有用性」**
塩谷隆信（秋田大学医学部）

15:20-15:30　質疑応答

15:30-15:50　休憩

15:50-16:30　**「高齢者の免疫能を強化するための栄養学的戦略」**
ステファニー･ブラム（スイス・ネスレリサーチセンター）

16:30-17:10　**「自立高齢者の老化遅延のための食生活」**
熊谷 修（人間総合科学大学）

17:10-17:20　質疑応答

17:20-17:30　**閉会の挨拶**
ジョン･ラフ（ILSI）

★Thursday, November 1

9:00- REGISTRATION

SESSION Ⅱ Fetal Nutrition and Risk of Life-style Related Diseases

Chair: Dr. Shuichi Kimura

9:30-10:10 **KEYNOTE LECTURE**
Prevention of Life-style Related Diseases in Childhood
Dr. Motoko Sakamoto, Wayo Women's University

Chair: Dr. Motoko Sakamoto

10:10-10:50 **Undernutrition during Pregnancy in Japan and Proposals for Its Improvement**
Dr. Hidemi Takimoto, National Institute of Public Health

10:50-10:55 Q & A

10:55-11:00 Coffee Break

11:00-11:40 **Intrauterine Undernutrition and Adult Obesity**
Dr. Hiroaki Itoh, National Hospital Organization Osaka National Hospital

11:40-12:20 **Nutritional Programming of Adult Disease**
Dr. Caroline McMillen, Sansom Institute, University of South Australia, Australia

12:20-12:30 Q & A

12:30-14:00 Lunch and Poster Session

SESSION Ⅲ The Role of Exercise and Nutrition Maintenance of QOL in People of Advanced Age

Chair: Dr. Shuhei Kobayashi, University of Human Arts and Sciences

14:00-14:40 **Diet and Lifestyle-related Diseases in the Elderly**
Dr. Satoshi Sasaki, National Institute of Health and Nutrition

14:40-15:20 **Effectiveness of Nutritional Support and Exercise Training in Patients with Stable COPD**
Dr. Takanobu Shioya, Akita University School of Health Sciences

15:20-15:30 Q & A

15:30-15:50 Coffee Break

15:50-16:30 **Decline of Immune Function in the Elderly and Recovery by Nutrition**
Dr. Stephanie Blum-Sperisen, Nestlé Research Center, Switzerland

16:30-17:10 **Dietary Habits to Postpone Aging Itself in Old Age**
Mr. Shu Kumagai, University of Human Arts and Sciences

17:10-17:20 Q & A

17:20-17:30 **CLOSING REMARKS**
Mr. John Ruff, ILSI, USA

【サテライト・シンポジウム】

★11月2日（金）

9:00-　受付・登録

午前の部　座長　西島基弘（実践女子大学）

9:30-10:00　**【基調講演】**
「食品の安全と安心のためのリスクアナリシス」
唐木英明（東京大学名誉教授）

10:00-10:30　**「食品成分／素材についての安全性評価の考え方」**
林 裕造（財団法人 日本健康栄養食品協会）

10:30-10:45　休憩

10:45-11:15　**「ビタミン類の摂取上限値の決定に至る根拠」**
柴田克己（滋賀県立大学）

11:15-11:45　**「ミネラルの摂取量の設定」**
イアン・C・ムンロ（カナダ・CANTOX）

11:45-12:15　**「特定保健用食品の安全性評価の考え方」**
池上幸江（大妻女子大学）

12:15-12:45　**「ポリフェノール類の一日摂取許容量の考え方」**
金沢和樹（神戸大学大学院農学研究科）

12:45-13:50　昼食

午後の部　座長　デイビッド・ベーカー（米国・イリノイ大学）

13:50-14:00　**「アミノ酸ワークショップの概要」**
デニス・ビアー（米国・小児栄養研究センター）

14:00-14:30　**「栄養素の安全な上限摂取量の設定に対する規制当局の考え方」**
クリスティン・L・テイラー（米国・全米科学アカデミー・医学研究所）

14:30-15:00　**「許容上限摂取量（UL）に対する業界の見解―発展させた評価法のビタミン、ミネラル、生理活性物質およびアミノ酸への応用」**
ジョン・N・ハスコック（米国・米国栄養評議会）

15:00-15:30　**「現行データからアミノ酸の安全な上限摂取量を設定するための検討事項：アミノ酸摂取量の上限を定義する方法」**
ポール・B・ペンチャルズ（カナダ・トロント大学）

15:30-15:45　休憩

15:45-16:25　**「アミノ酸過剰のバイオマーカー候補物質」**
坂井良成（味の素㈱ライフサイエンス研究所）

16:25-17:25　午後の部の討論
座長　リュック・シノベール（フランス・パリ第五大学）

【SATELLITE SYMPOSIUM】

★Friday, November 2

9:00-	RESISTRATION
	Chair: Dr. Motohiro Nishijima, Jissen Women's Educational Institute
9:30-10:00	【KEYNOTE LECTURE】 **Risk Analysis for Safety of Foods and Ease of Mind of Consumers** Dr. Hideaki Karaki, The University of Tokyo
10:00-10:30	**A Consideration for Evaluating the Safety of Food Ingredients and Materials** Dr. Yuzoh Hayashi, Japan Health Food & Nutritional Association
10:30-10:45	Coffee Break
10:45-11:15	**Evidences to Decision of Tolerable Upper Intake Levels of Vitamins** Dr. Katsumi Shibata, The University of Shiga Prefecture
11:15-11:45	**Setting Levels for Minerals** Dr. Ian C. Munro, CANTOX, Canada
11:45-12:15	**Basic Principles for Safety of "Food for Specified Health Uses"** Dr. Sachie Ikegami, Otsuma Women's University
12:15-12:45	**A Way of Thinking for Allowance of Daily Intake of Dietary Polyphenols** Dr. Kazuki Kanazawa, Graduate School of Agriculture, Kobe University
12:45-13:50	Lunch
	Chair: Dr. David Baker, University of Illinois, USA
13:50-14:00	**Brief Introduction of AAAWs** Dr. Dennis Bier, Children's Nutrition Research Center, USA
14:00-14:30	**A Regulatory Standpoint for Establishing Upper Levels of Safe Intake for Nutrients** Dr. Christine L. Taylor, Institute of Medicine, National Academies of Science, USA
14:30-15:00	**Industry View of UL-Application of Expanded Method to Vitamins, Minerals, Bioactive Substances, and Amino Acids** Dr. John N. Hathcock, Council for Responsible Nutrition, USA
15:00-15:30	**Considerations for Safe Upper Limits of Amino Acids from Current Data - An Approach to Defining the Upper Limits of Amino Acid Intake -** Dr. Paul B. Pencharz, University of Toronto, Canada
15:30-15:45	Coffee Break
15:45-16:25	**Possible Biomarkers for Amino Acid Excess Determination** Dr. Ryosei Sakai, Institute of Life Sciences, Ajinomoto, Co., Inc.
16:25-17:25	Discussion Chair: Dr. Luc Cynober, University of Paris 5, France

第5回「栄養とエイジング」国際会議
ヘルシーエイジングを目指して～ライフステージ別栄養の諸問題

2007年10月31日、11月1日
国際連合大学 ウ·タント国際会議場（東京・青山）

主　催：International Life Sciences Institute（ILSI）
特定非営利活動法人 国際生命科学研究機構（ILSI Japan）

共　催：ILSI北米支部（ILSI North America）
ILSIヨーロッパ支部（ILSI Europe）
ILSI中国事務所（ILSI Focal Point in China）
ILSI 東南アジア支部（ILSI SEA）
国際アミノ酸科学協会（ICAAS）

後　援：厚生労働省
農林水産省
東京都
社団法人 日本農芸化学会
日本基礎老化学会
日本臨床栄養学会
社団法人 日本栄養·食糧学会
社団法人 日本栄養士会
日本応用老年学会

セッションⅠ-1　【基調講演】

肥満と生活習慣病、食品産業の役割

渡邊　昌
独立行政法人 国立健康・栄養研究所　理事長

現在、わが国は世界にも例を見ないスピードで高齢化社会に移行しており、厚生労働省は健康寿命の延伸をテーマに、2000年より「健康日本21」運動を展開している。しかし、中間評価では達成された目標は少なく、糖尿病をはじめ、高血圧、高脂血症など生活習慣病と呼ばれる疾患は増加し、医療費の増大にも歯止めがかかっていない。

これらの疾患の発症や悪化には、「内臓脂肪型肥満」が大きな関わりを持つことが明らかになってきた。この「内臓脂肪型肥満」に加え、血糖値、血圧、血清脂質のうち二つ以上に異常がある場合、将来の循環器疾患となるリスクが高く、メタボリックシンドローム(内臓脂肪症候群)として概念がまとめられた。

メタボリックシンドロームになると、動脈硬化が年齢相応より早く進行し、狭心症や心筋梗塞、脳梗塞のリスクが大きくなる。つまり狭心症や心筋梗塞、脳梗塞の上流にメタボリックシンドローム（内臓脂肪症候群）があり、さらにその上流に内臓肥満がある。

2004年に実施した国民健康・栄養調査から推計すると、40～74歳の中高年約5,700万人のうち、940万人がメタボリック症候群に、1,020万人が予備群になる。男女別では、男性が2人に1人、女性で5人に1人が、メタボリックシンドローム予備群に該当し、男性の方がその割合が極めて高い。厚労省は、老人保健法の改正により、2008年度から40歳以上の健診を大幅に見直す方針を打ち出している。予備軍の段階での保健指導を強化し、薬による治療が必要になる前に、受診者の生活習慣を変えるよう促す考えである。生活習慣病の予防には肥満解消がもっとも効果的であり、それには栄養指導、運動指導が必要である。しかし、社会全体が環境整備をする必要があり、食品の製造、供給をする食品産業、外食産業の役割が大きい。子供時代からの肥満対策に食育基本法も期待されている。これら日本の環境を含めて講演したい。

SESSION I - 1 【KEYNOTE LECTURE】

Obesity and Life-style Related Diseases in Japan: Roles of Food Industry

Shaw Watanabe, M.D., Dr.Med.Sci.
Director-General, National Institute of Health and Nutrition

In response to rapid shift to aging society at an unprecedented pace in Japan, the Ministry of Health, Labour and Welfare has been implementing the national health promotion program called "Health Japan 21" across the country since 2000. The mid-term evaluation of "Health Japan 21" showed, however, that few goals have been achieved so far. The reality is that the morbidity of lifestyle-related diseases, such as diabetes, hypertension and hyperlipidemia increased, and no action has been taken yet to curve the increased medical expenditure.

It has been recently explored that visceral fat obesity is strongly associated with development and progress of the above mentioned diseases. Based on which, "metabolic syndrome (visceral fat syndrome)" is now defined as the conditions where one has abnormal levels in more than two out of blood glucose, blood pressure and serum lipid, in addition to visceral fat obesity. When one develops metabolic syndrome, atherosclerosis would progress rapidly for his/her age, which would eventually lead to an increased risk of angina, myocardial infarction and stroke. In other words, angina, myocardial infarction and stroke can be caused by metabolic syndrome, which would result from accumulated visceral fat.

According to the National Health and Nutrition Survey in 2004, out of 57,000,000 people aged 40-74 years, 9,400,000 and 10,200,000 are estimated as metabolic syndrome and prodromal metabolic syndrome respectively. These figures, therefore, indicate that one in two males and one in five females have prodromal metabolic syndrome, hence higher risk in male. Under this circumstance, following the revision of Health and Medical Service Law for the Aged, the Ministry of Health, Labour and Welfare is going to launch a new health monitoring and evaluation system targeting population aged 40 years or over from the fiscal year of 2008.

By enhancing health guidance at the prodromal stage, this new system aims to improve one's lifestyle behaviors before she/he develops the symptoms in need of medicine. Obesity control is the most effective measure to prevent lifestyle-related diseases, for which appropriate dietary and exercise guidance are required. More importantly, the food environment in the whole society should be improved, where food industry and food service industry would take an important role. Besides, it is expected that the Basic Act on Shokuiku could facilitate obesity control from an early age. I would like to make a speech focusing on the current food environment in Japan.

セッションI-2

メタボリックシンドロームの分子機構と治療戦略

門脇　孝
東京大学大学院医学系研究科糖尿病・代謝内科 教授

メタボリックシンドロームは糖尿病・高脂血症・高血圧が1人の患者に重積する病態で、心血管病の非常に重要な危険因子である。現在、世界の人口の20-25%がメタボリックシンドロームに罹患している。高脂肪食や運動不足などの生活習慣によって、肥満・内臓脂肪蓄積が惹起され、その結果、脂肪細胞から分泌されるアディポネクチンが低下することがインスリン抵抗性・糖尿病・メタボリックシンドロームの成因として重要である。私共はアディポネクチンの作用を伝達すると考えられるアディポネクチン受容体（AdipoR1、AdipoR2）を同定した。このAdipoR1、AdipoR2、及びAdipoR1/ AdipoR2欠損マウスを作成し、これらのアディポネクチン受容体がインスリン感受性と血糖の調節に必須であること、またAdipoR1とAdipoR2がアディポネクチンの主要なシグナル受容体であることを示した。更に、肥満に伴う糖尿病では肝臓でAdipoR1とAdipoR2が低下しており、これを補充するだけで、糖尿病が改善することを明らかにした。糖尿病・メタボリックシンドロームの遺伝的素因についても、PPARγ、アディポネクチン、HNF4α、TCF7L2などの遺伝子多型を明らかにした。分子病態や遺伝素因に基づく糖尿病・メタボリックシンドロームの分子標的治療法やオーダーメイド治療・予防法の開発についても述べたい。

文献
1）*Nature* 372: 182-186, 1994, 2）*Nature Medicine* 7: 941-946, 2001, 3）*Nature Medicine* 8: 856-863, 2002,
4）*Nature* 423: 762-769, 2003, 5）*Nature Medicine* 13: 332-339, 2007, 6）*Cell Metabolism* 6: 1-14, 2007

SESSION I -2

Metabolic Syndrome: Pathophysiology and Treatment Strategy

Takashi Kadowaki, M.D., Ph.D.
Professor, Dept. of Metabolic Diseases, Graduate School of Medicine, The University of Tokyo

Metabolic syndrome is characterized by a constellation of diabetes, hyperlipidemia and hypertension, and represents a major cause of cardiovascular disease. It is estimated that around 20-25 per cent of the world's adult population have the metabolic syndrome. This pandemic of metabolic syndrome is caused by the pandemic of obesity and visceral fat accumulation via increased fat intake and sendentary lifestyle worldwide. Adiponectin is a fat-specific hormone which sensitizes the body to insulin. Targeted disruption of adiponectin show features of metabolic syndrome such as insulin resistance, glucose intolerance, hypertriglyceridemia, and hypertension. Obesity is also associated with down-regulation of adiponectin, which is causally involved in obesity-linked insulin resistance and metabolic syndrome. Obesity is also associated with down-regulation of adiponectin receptors and adiponectin resistance. In an attempt to identify agonists toward adiponectin receptors, we have recently identified osmotin, a plant defense protein, can bind and activate mammalian adiponectin receptors. In this symposium, I will discuss the burden of obesity, metabolic syndrome and diabetes in people worldwide and the strategy to combat pandemic of these conditions. In addition, I will talk about recent advances on molecular mechanisms and treatment strategies of insulin resistance, metabolic syndrome and cardiovascular diseases with an emphasis on the adiponectin pathway.

1) ***Nature*** 372: 182-186, 1994, 2) ***Nature Medicine*** 7:941-946, 2001, 3) ***Nature Medicine*** 8: 856-863, 2002,
4) ***Nature*** 423: 762-769, 2003, 5) ***Nature Medicine*** 13: 332-339, 2007, 6) ***Cell Metabolism*** 6: 1-14, 2007

セッションⅠ

セッションⅠ-3

テーラーメイド栄養学

坂根　直樹
独立行政法人 国立病院機構京都医療センター臨床研究センター　室長

本邦でも食生活の近代化に伴い、2型糖尿病・高脂血症・高血圧などの生活習慣病が増加している。その基盤となる肥満対策が重要である。日本人はもともと内臓脂肪が蓄積しやすく、糖尿病が発症しやすい民族とされる。内臓脂肪型肥満はエネルギーのアンバランスを特徴とするが、遺伝と環境の相互の影響を受ける。双生児の過食や食事制限による個人間の反応に関する興味深い研究がいくつかある。過食により体重が増加しやすい者や他の者より減量が容易である者がいるが、その場合には同じ遺伝子タイプを持つ者は同じように反応することがら、食事に対する反応性は遺伝子によって規定されている可能性がある。さらに、候補遺伝子による食事と遺伝子の相互作用に関するエビデンスも集積されつつある。エネルギー代謝や摂食に関わる遺伝子が肥満になりやすさと関係している。2005年までに、関連研究により127の候補遺伝子が肥満と関連あるとされる。10以上の研究で肥満と関連があるとされたのは、PPARγ、β_3-アドレナリン受容体（ADRB3）、β_2-アドレナリン受容体（ADRB2）、レプチン受容体（LEPR）、G蛋白β3サブユニット（GNB3）、脱共役タンパク質3（UCP3）、アディポネクチン（ADIPOQ）、レプチン（LEP）、UCP2、セロトニン受容体2C（HTR2C）、グルココルチコイド受容体（NR 3 C1）、UCP1 の12遺伝子である。ADRB3は内臓脂肪と褐色脂肪組織に主に存在し、脂肪分解と熱産生に関わると考えられている。一方、米国アリゾナ州居住のピマ族は肥満9割、糖尿病5割以上で、遺伝子研究がされている。ピマ族ではADRB3（Trp64Arg）多型の頻度が高く、本多型を持つ者は2型糖尿病になるのが早まるとともに代謝量の低下傾向がみられる。また、日本人はエスキモー、ピマ族についでその頻度が高く、内臓脂肪型肥満やインスリン抵抗性、減量困難性と関連している。減量が困難な理由として、安静時代謝量の低下と脂肪分解能の低下が考えられている。日本人におけるメタ解析ではBMIを0.26kg/m^{2}増加させる。しかし、オーストラリア人ではこの多型は妊よう性との関連することが示されている。飢餓の時代には生き延びるために必要であった倹約遺伝子が、飽食の現代では内臓脂肪の蓄積や糖尿病の増加と関連しているのかもしれない。実際、ピマ族に肥満が増えたのは第二次世界大戦後、ハンバーガーの味を覚え、貧困のため小麦粉、砂糖、油が支給されてからである。今も農耕をしているメキシコのピマ族は平均体重が26kg少なく、糖尿病の発症率も低い。最近、Miyakiらは本多型を持つ者は高エネルギー摂取時に肥満リスクを増加させると報告している。他にもUCP1（-3826A/G）を持つ者は高糖質食摂取後の熱産生には差は認めないが、高脂肪食摂取後の熱産生能が低下しており、高脂肪食を続けていると将来肥満する可能性がある。逆に、ADRB2(Arg16Gly)を持つ者は脂肪分解能が亢進しており、やせやすい。また、骨格筋に発現するUCP3（-55C/T）を持つ者は肥満リスクが低い。日本糖尿病予防プログラム（JDPP）や我々の減量プログラムにおいても、食事介入による体重、脂質、血圧の低下には遺伝子多型が関与している。日本人は倹約遺伝子を持ち、膵臓のインスリン分泌能が低く、アルコールに弱いなどの特徴がある。これから食事と遺伝子の相互作用に関するエビデンスが集積してくることであろう。今後は、患者さんの遺伝的背景も考慮した食事アドバイス、テーラーメイド栄養学が求められる。

SESSION I -3

Tailor-made Nutrition

Naoki Sakane, Ph.D.
Professor, National Hospital Organization Kyoto Medical Center

An increasing number of lifestyle disorders such as type 2 diabetes mellitus (T2DM) and hyperlipidemia have emerged in response to the rapid urbanization that has occurred in Japan. Japanese are prone to accumulate visceral fat and develop T2DM. Obesity is a multifactorial condition, most often due to an imbalance in energy intake and expenditure. Susceptibility to obesity is partly determined by genetic factors, but an "obesity-promoting environment" is typically necessary for its phenotypic expression. A few well-controlled studies with monozygotic twins have specifically addressed the genetic background of interindividual variation in response to overfeeding or energy restriction. Some individuals will gain or lose weight more easily than others, but subjects sharing the same genotype (monozygotic twins) will respond in a similar way, suggesting that the responsiveness to diet is mediated by their genotype. Further evidence for gene-diet interactions comes from candidate gene studies. Genes involved in pathways regulating energy expenditure and food intake may play a role in the predisposition to obesity. The majority of the 127 candidate genes associated with obesity have been identified in association studies. Candidate genes, that have shown associations with obesity-related phenotypes in at least 10 studies, include PPARG, ADRB3, ADRB2, LRPR, GN3B, UCP3, ADIPOQ, LEP, UCP2, HTR2C, NR3C1, and UCP1. ADRB3 is mainly expressed in visceral fats and brown adipose tissues and is considered responsible for lipolysis and thermogenesis. The Pima Indians, who migrated from central Asia to Arizona in the USA through Mexico about 38,000 years ago, were selected for a search of polymorphisms, because more than half of its population develop obesity and diabetes. Pima Indians have a high frequency of this polymorphism, and those with the polymorphism demonstrate an early onset of T2DM and a tendency toward a low metabolic rate. Japanese have the third-highest frequency in the world behind Alaskan Eskimos and Pima Indians. This polymorphism is also associated with visceral obesity and resistance to insulin, an increased capacity to gain weight, and difficulty in weight loss. Meta-analysis in Japanese shows that the weighted mean difference in BMI was 0.26 kg/m^2, indicating that those with the polymorphism exhibited higher BMI than normal homozygous subjects. The hypothesis of an advantage provided by this polymorphism include earlier menarche, which may result in a longer period of fertility in Australians with this polymorphism. However, the "thrifty" genotype and phenotype that saves energy are detrimental to the health of people living in affluent societies. Miyaki et al. reported that the presence of the polymorphism alone does not significantly increase the risk of obesity. However, high energy intake interacts with the polymorphism and leads to a significant increase in the risk of obesity. The Japan Diabetes Prevention Program and the behavioral weight-loss program show that the success of lifestyle intervention depends on the polymorphisms of those genes that are suggested to play a role in energy metabolism, lipid metabolism, insulin resistance or insulin secretion. Accelerating research on gene-diet interactions is likely to contribute interesting information that may lead to further individualized dietary guidance in the future.

セッションⅠ

セッションⅠ-4

動脈硬化性疾患の一次予防――メタボリックシンドロームを含めて――

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背景

日本におけるエビデンスベースの高コレステロール血症治療は、日本人の患者集団における直接的なエビデンスがないために確立されていなかった。我々の目的は、食事療法もしくはプラバスタチンを併用した食事療法がメタボリックシンドロームと関連した、あるいは非関連の心血管イベントの発症を減少させるか否かを検証することであった。

方法

この前向き、無作為化、オープンラベルのブラインド試験では、高コレステロール血症（総コレステロール220-270mg/dL）患者で、冠動脈性心疾患や脳卒中の病歴がない方を、食事療法のみの群と、食事療法に加え、10-20mg/dのプラバスタチンを摂取する群に無作為に割り付けた。プライマリーエンドポイントは冠動脈性心臓病の初発とした。統計解析はインテンション ツー トリート（Intention to treat）の手法により行なった。また、日本のメタボリックシンドローム判定基準（Jp-Mets）と米国のNCEP基準（US-Mets）を用いて、サブ解析も行った。

結果

3,966人が食事療法のみの群へ、3,866人がプラバスタチン併用の食事療法群へと無作為に振り分けられた。平均追跡期間は5.3年であった。食事療法単独群とプラスプラバスタチン併用群で、平均の総コレステロールはそれぞれ、2.1%、11.5%減少し、平均のLDLコレステロールはそれぞれ3.2%、18.0%減少した。冠動脈性心臓病の発症は、プラバスタチン併用群において、食事療法単独群より有意に少なかった（66例 vs 101例；HR0.67、NNT119、P=0.01）。

食事療法単独群では、心血管症状のイベント発症率を抑制するのに8%以上のLDLコレステロールの減少を要した。

メタボリックシンドロームではない被験者と比べて、（Jp-Mets、US-Metsに基づいた）メタボリックシンドロームの被験者は、CHDの発症率が1.8倍増加し、脳卒中の発症率は約2.3倍増加することが認められた。

結論

日本において、プラバスタチンの低用量投与を用いた治療は、冠動脈性心疾患と脳卒中のリスクを減少させた。メタボリックシンドロームの被験者においては、プラバスタチンにより脳卒中の発症が減少した。

SESSION I -4

Primary Prevention of Artherosclerotic Vascular Diseases in Japan with Special Reference to Metabolic Syndrome

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Background

Evidence-based treatment for hypercholesterolemia in Japan has been hindered by the lack of direct evidence in this population. Our aim was to assess whether the treatment with diet or diet plus pravastatin could reduce the incidence of cardiovascular events with or without metabolic syndrome.

Methods

In this prospective, randomized, open-labelled, blinded study, patients with hypercholesterolemia (total cholesterol 220-270mg/dL) and no history of coronary heart disease or stroke were randomly assigned diet or diet plus 10-20 mg pravastatin daily. The primary endpoint was the first occurrence of coronary heart disease. Statistical analyses were done by intention to treat. Sub-analysis was also made by using the criteria of Japanese metabolic syndrome (Jp-Mets) and NCEP (US-Mets).

Findings

3966 patients were randomly assigned to the diet group and 3866 to the diet plus pravastatin group. Mean follow-up was 5.3 years. Mean total cholesterol was reduced by 2.1% and 11.5% and mean LDL cholesterol by 3.2% and 18.0% in the diet and the diet plus pravastatin groups, respectively. Coronary heart disease was significantly lower in the diet plus Pravastatin group than in the diet alone group (66 events vs 101 events; HR 0.67, NNT 119, P=0.01).

In the diet alone group, more than 8% reduction of LDL cholesterol was required to suppress the incidence of cardiovascular events.

Increased incidence of CHD by about 1.8 times and stroke by about 2.3 times were observed in the subjects (Jp.Mets, US-Mets) compared to the subjects without metabolic syndrome.

Conclusion

Treatment with a low dose of pravastatin reduces the risk of coronary heart disease and stroke in Japan. Stroke incidences were reduced by pravastatin in the subjects with metabolic syndrome.

セッションⅠ

セッションⅠ-5

小児のメタボリックシンドロームとその診断基準

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メタボリックシンドロームは動脈硬化性疾患である心筋梗塞や脳血管障害などの発症と深くかかわり、現代医療の主要なテーマの一つとなってきた。内臓脂肪の蓄積はメタボリックの本質的な要因であり、肥満診療の意義が再確認される。

小児におけるメタボリックシンドロームの意義は以下のような点があげられよう。（1）メタボリックシンドロームと考えられる病変が小児においても認められる、（2）成人のメタボリックシンドロームのかなりの部分が小児期の肥満ないしメタボリックシンドローム予備群から生ずる、（3）世界的に小児肥満の頻度は近年も増加傾向が続いている、（4）生活習慣の確立は小児期にスタートする、（5）小児においても肥満・メタボリックシンドロームにより徐々に血管の病変が進行するとのエビデンスがより集積しつつあるなどがその意義としてあげられる。

我が国における小児肥満（標準体重+20%以上）の頻度は1968年では小学生の全国平均で2.3／2.8%（男／女）であった。近年の統計によれば8～10%程度と3～4倍程度の増加が見られる。以前は人口密度の高い都市部により高頻度であり、非都市部ではより低率であったが、最近の傾向としては広く全国的に増加している。欧米でもIOTFの調査では対象国すべてで増加しておりBritish Medical Associationの統計を例にあげれば、6～10歳の過体重の英国女児は30%前後である。

1995年に脂肪細胞においてレプチンの存在が報告されて以来、アディポサイトカインと呼ばれるいくつかの活性ペプチドが発見された。脂肪細胞はそれまで考えられていたエネルギー貯蔵の役割のみでなく、各種の内分泌機能を有することが明らかとなった。

厚生労働省も早期からの生活習慣病対策を重視し「小児期メタボリックシンドロームの概念・病態・診断基準の確立及び効果的介入に関するコホート研究（主任研究者：大関武彦）」が平成17年度から開始された。内臓脂肪についての腹囲の基準としては、肥満小児における合併症出現リスクが統計学的に上昇する値、肥満のない小児における標準範囲の２つの方向から検討し基準を設定した。（1）腹囲の増加（80cm以上）、（2）中性脂肪120 mg/dl以上ないしHDL-コレステロール40 mg/dl未満、（3）収縮期血圧125 mmHg以上ないし拡張期血圧70 mmHg以上、（4）空腹時血糖100 mg/dl以上の項目のうち（1）を必須とし（2）～（4）のうちの2つを含む場合に診断される。腹囲／身長が0.5以上である場合は同様に内臓脂肪の蓄積と判断される。

メタボリックシンドロームは動脈硬化性疾患の発症と関連し、その予防や支援は大きな意義を有する。小児期からの介入・予防は、小児のみならずその後の成人期のメタボリックシンドロームの予防にとって極めて重要な時期といえる。

SESSION I -5

Metabolic Syndrome and Its Diagnostic Criteria for Japanese Children and Adolescents

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In recent years, more reports have demonstrated significant relation between atherosclerotic disorders, such as cerebrovascular disorders and coronary infarction, and metabolic syndrome, which is now one of the most essential medical topics in Japan as well as North America and Europe. Visceral adiposity has been listed as the causative factor. Obesity in children is caused by genetic and environmental factors, and probably by epigenetic mechanism.

Metabolic syndrome in children and adolescents seems to have clinical significance because (1) boys and girls with metabolic syndrome were found as early as in childhood, (2) adults with metabolic syndrome were obese while they were young, (3) the prevalence of childhood obesity has been increasing in developed countries, (4) childhood is an essential period to establish one's lifestyle, (5) vascular pathology was demonstrated even in younger ages.

Prevalence of obesity (120% of the standard weight or heavier) in Japanese children attending elementary schools was 2.3/2.8% (boys/girls) in 1960s. Recent reports showed the prevalence of 8 to 10%, and it means 3-4 times increment during the past 40 years. Higher prevalence was reported in urban areas as compared to rural areas in some previous studies. However, obese children were demonstrated universally throughout the country in recent years. British Medical Association warned that overweight boys and girls were about 30% among the children with the same age. In the United States and other European countries, similar increment has been observed.

Since the first documentation of leptin in 1995, numbers of biologically active peptides, adipocytokines (adipokines), have been found. Adipocytes are cells not only storing energy, as previously known, but also having various endocrine functions. Augmentation of abdominal adiposity is accompanied by changes in secretion and serum levels of adipocytokines. The changes appear to promote metabolic and cardiovascular abnormalities.

The Japanese Ministry of Health, Labor and Welfare understands significance of earlier intervention for "Life-style-related disorders" and started in 2005 a scientific project entitled "A cohort study for concept, pathophysiology, establishment of diagnostic criteria and effective intervention for metabolic syndrome in children (chief: Takehiko Ohzeki). The diagnostic criteria are proposed as follows: (1) Abdominal circumference 80 cm or more, (2) Serum triglyceride level 120 mg/dl or higher and/or HDL-cholesterol level lower than 40 mg/dl, (3) Systolic blood pressure 125 mmHg or higher and/or diastolic 75 mg/dl or higher, (4) Fasting plasma glucose 100 mg/dl or higher. Children who has criterion (1) and 2 of the others are diagnosed as having metabolic syndrome. If addition abdominal circumference/height is 0.5 or higher, the subject is considered to have criterion. For assessment of visceral adiposity, abdominal circumference has been measured because it can be applied easily The criterion for abdominal circumference (80 cm) was set on the basis of two studies for obese and normal weight children and adolescents.

Metabolic syndrome should be studied more precisely because it is one of the most important causes of atherosclerosis and intervention to the individuals with the syndrome seems of great significance. Lifestyle in children is related with that in adults and it is essential for establishing proper lifestyle during childhood to promote health throughout the life.

セッションⅠ

セッションⅠ-6

歯周病と体の健康に関連した研究の概要

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歯周病は、この20年間、糖尿病、心臓病、未熟児出産のような様々な体の病気およびホルモン、ストレスや喫煙など体に害を与えるような様々な変化と関連があると考えられてきた。入手した文献によると、最も証明されているのは、糖尿病と歯周病の関係であるが、一方、心臓病との関係についての証拠は現在増えており、母体の健康との関係についての根拠は減ってきている。横断研究から縦断研究にまたがる口腔の健康と体の病気の間の相互関係についての重要な文献があり、それは、歯周病が与える体の病気へのリスクが増えることを指摘している。この観察された関係は、基本的な介入試験研究、つまり歯周病と体の病気の治療を受けている患者は、しかしながら多くの場合、（心臓発作や死などの）臨床的な最終点ではなく、唯一病気の代わりである症状だけで改善しているという、利用可能な介入試験研究によって、一般的に確認され、その情報が伝わっている。

心臓病については、多くの研究がCRP、サイトカイン、フィブリンなどのような分子と関係のある病気が、体と口腔の健康の関係の指標であると考えている。同様に糖尿病、インシュリン抵抗性、血糖コントロールおよびAGEs、RAGEs、脂質、ホルモン、サイトカインのような分子と関係のある病気のそれらのレベルは、口腔と体の健康の関係の指標である。

このように、この発表は決定的に口腔と体の健康に関する研究の知見について焦点をあてる。そして、現存するデータの強み、私たちの知識の相違点や情報のもつ重大性や予想される影響、さらに効果的な健康情報と将来の政策の必要性に焦点をあてながら、起こりうる一般的な病気のメカニズムを考えていく。

SESSION I -6

Overviews of the Links between Periodontal Disease and Systemic Health

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Periodontal Disease has in the last two decades been associated with a variety of systemic diseases including Diabetes, Cardiovascular Disease, Pre-term births and a variety of systemic modifiers including hormones, stress and smoking. The most established of these in terms of the available literature is the relationship between diabetes and periodontal disease, but the evidence for links with cardiovascular disease is currently growing and with maternal health diminishing. There is now substantial literature on the relationship between oral health and systemic disease ranging from cross-sectional and longitudinal studies most of which indicate an increased risk of systemic disease in periodontitis affected subjects. Such observed relationships are typically confirmed and extended by rudimentary intervention studies where patients are treated for periodontitis and their systemic health improves however in many cases only surrogate markers of disease and not clinical end-points (such as stroke, death etc) can be utilized. In cardiovascular disease, numerous studies consider disease related molecules such as CRP, cytokines, fibrin etc to indicate relationships between these and systemic and oral health. Similarly in diabetes, insulin resistance, glycemic control and levels of disease related molecules such as AGEs and RAGEs, lipids, hormones and cytokines are indicative of oral and systemic health relationships. Thus this presentation will critically address research findings in oral and systemic health and consider possible common disease mechanisms, focusing on the strength of existing data, gaps in our knowledge and the significance and implications of this information and need for effective health communication and future policy.

セッションⅠ-7

ペプチドによる神経性の摂食調節機構

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摂食は、末梢と中枢で産生される摂食亢進物質と抑制物質の複雑な相互関係により、巧妙に調節されている。視床下部は、このような末梢や脳の他の領域からの摂食調節情報を統合する中枢である。脂肪組織から分泌される摂食抑制蛋白質 レプチン、胃からの亢進ペプチド グレリン、腸からの抑制ペプチド コレシストキニン、GLP-1、ペプチドYYなどの末梢で産生される物質が、視床下部でどのように作用しているか、その細胞生理学・形態学的基盤が解明されつつある。視床下部では神経ペプチドY、グレリン、オレキシン、ガラニン、GALP、POMC、CART、AgRP、CRF、バゾプレシン、TRHなどのペプチドが生合成され、摂食物質に機能している。行動薬理学的実験や遺伝子操作マウスの作出とその解析、ヒトにおける肥満や痩せでの解析などを通じて、これらの物質の臨床的意義も明らかにされつつある。中枢と末梢を結ぶ摂食調節機構に関する研究は、急速に進展しつつあり、摂食とエネルギー代謝調節に関わる新規の視床下部ペプチドの探索を含め、ペプチドと摂食調節ニューロンとの関連について発表する

SESSION I -7

Neuronal Mechanisms of Feeding Regulation by Peptides

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Energy balance is controlled by the complicated and minute interactions of substances to stimulate or suppress food intake and energy expenditure. The molecular mechanisms of energy balance are coming to light by the recent robust progresses in the molecular biology and neuroscience. Hypothalamus, the center of energy homeostasis, receives information related to satiety and fast from the body and other brain regions, integrate them, and mediate interactions with efferent pathways. We have identified peptide ligands for orphan G-protein coupled receptors and studied their physiological and clinical implications in the regulation of energy homeostasis. We have clarified that the vagal afferent is the major pathway conveying signals of gut hormones to the brain. These findings will provide a clue to our better understanding of the molecular etiology of body weight control and the pathogenesis of obesity and anorexia in humans.

セッションⅠ-8

機能性食品とエネルギーの消費

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スパイス入りの食品やハーブ飲料の摂取は熱産生を高め、場合によっては満腹感を向上させる。このような観点から好例として挙げられるのは、カプサイシン、ブラックペッパー、ショウガ、ミックススパイス、緑茶、紅茶、カフェインなどである。これらの機能性成分は、満腹感や熱産生、脂肪の酸化といった肥満の予防や治療の代謝ターゲットに対して、有意な効果をもたらす可能性がある。熱産生の増大は、異なったメカニズムが相乗的に作用することにより生じると考えられている。例えば、それぞれの成分がホスホジエステラーゼによるｃAMPの分解を抑制したり、カテコールアミンの交感神経からの分泌を増強したりするといったことが挙げられる。しかし、エフェドリンの副作用はこのようなアプローチの可能性を阻んでいる。カプサイシンは有効であるとされているが、臨床的に用いられる場合、現段階では、非現実的なレベルの量を投与することが要求されている。また、体重管理におけるプラスの効果は緑茶混合物の使用でも示されている。緑茶は茶カテキンとカフェインの両方を含むため、カテコールO-メチルトランスフェラーゼの抑制、およびホスホジエステラーゼの抑制により作用すると考えられる。ここでもそのメカニズムは、相乗的に作用している可能性が考えられる。さらに茶カテキンは、過体重や肥満の進展を防ぐといわれている抗血管新生作用を持っている。その上、交感神経系は脂肪分解の調節に関与しており、白色脂肪組織の交感神経支配は一般的に、全身脂肪の調節において重要な役割を果たすと考えられている。熱産生を誘導する成分は、エネルギーの蓄積と肥満の予防に役立つ機能性成分であると考えられる。

SESSION I -8

Functional Food and Energy Expenditure

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Consumption of spiced foods or herbal drinks leads to greater thermogenesis and in some cases to greater satiety. In this regard, capsaicin, black pepper, ginger, mixed spices, green tea, black tea and caffeine are relevant examples. These functional ingredients have the potential to produce significant effects on metabolic targets for prevention and treatment of obesity, such as satiety, thermogenesis, and fat oxidation. The higher thermogenesis is likely due to different mechanisms that may operate synergistically, e.g. respectively inhibiting the phosphodiesterase-induced degradation of cAMP and enhancing the sympathetic release of catecholamines. However adverse effects of ephedrine prevent the feasibility of this approach. Capsaicin has been shown to be effective, yet when it is used clinically it requires a strong compliance to a certain dosage that has not been shown to be feasible yet. Also positive effects on body-weight management have been shown using green tea mixtures. Green tea, by containing both tea catechins and caffeine, may act through inhibition of catechol O-methyl-transferase, and inhibition of phosphodiesterase. Here the mechanisms may also operate synergistically. In addition, tea catechins have anti-angiogenic properties that may prevent development of overweight and obesity. Furthermore, the sympathetic nervous system is involved in the regulation of lipolysis, and the sympathetic innervation of white adipose tissue may play an important role in the regulation of total body fat in general. Thermogenic ingredients may be considered as functional agents that can help preventing a positive energy balance and obesity.

セッションⅡ-1　【基調講演】

小児期における生活習慣病予防

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がん、心臓疾患のような生活習慣病は、全死亡例の60％以上を占めわが国の主要な健康問題の一つとなっている。第一、第二、第三の予防法、治療の進歩、専門家の育成などが積極的に進められている。

近年、生活習慣病の発生は胎児期の低栄養状態が高血圧、高脂血症、動脈硬化、糖尿病、認知能の低下の発症がプログラムされているという説から、妊娠期の母親の低栄養状態が低体重児の出生に影響することが憂慮されている。

血圧、肥満、血清コレステロール、HDL - コレステロール、および中性脂肪が心疾患のリスクファクターとされているが、これらの指標は同時に生活習慣病のリスクとして重要視されている。これらの指標が単に成人だけでなく、小児期に見られるという観察が始まってからかなりの期間が経っている。これらの要因が生活習慣及び食習慣によるものであることが明らかにされてから久しく、したがって成人になってからの予防ではなく、小児期から予防が重要であることは言うまでもない。しかしこれらの指標を対象とする検診はまだ国としては要求されておらず、これらを重要視する地域で任意に実施し、その後の教育、支援が実施されているのが現状である。

この報告は小児期からの健診とその後の栄養・生活指導を重要視した東京近郊の地域で1984年より25年にわたり、4 - 5歳、9 - 10歳ならびに12 - 13歳の同一の子どもを対象に毎年継続した健診とその後の結果をまとめたものである。

健診項目は身長・体重から肥満度を、血清検査ではコレステロール値、HDLコレステロール値、中性脂肪値、血圧、ヘモグロビン値をもとめ、健診時に食習慣調査、生活活動調査、また、異常値保有者への指導時により精度の高い食物摂取量調査を行った。これらの結果から、症候発現に影響する食物摂取および生活状況との関係を検討した。

出生時低体重児の4 - 5歳時の異常値への影響は、血清脂質値に有意の高値、8 - 9歳時にやや高めを示したが、12 - 13歳時では影響は見られなかった。年齢が高くなるに伴い、食生活や日常生活が正常に営まれる状況では影響は無いと判断される。

各指標の異常値出現率は年齢によって少しずつ傾向は異なるが、肥満および高コレステロールの出現率は8 - 9歳が最も高く、それぞれ約20％、と5～10％を示している。低HDLコレステロール値保有者の出現率は4 - 5歳児が最も高く、これは保育園における長い昼寝時間による運動量が少ないものと推測される。

異常値保有者には各年齢で母親同伴による個人指導を実施した。個人指導の成果は高く、指導した親子の60％から80％に異常値改善がみられるが、指導しなかった群にその後の健診で異常値が発現する例が多く見られた。しがたって、健診後の教育のあり方として個人指導のほかに保育園や学校で栄養教育の実践を続けてきた。

4 - 5歳時で最も保有者率が高かった年で46％であったものが、現在では29％と低値を示している。長期の教育支援の成果は年々異常値保有者の減少に現れてきている。

SESSION II -1 【KEYNOTE LECTURE】

Prevention of Life-style Related Diseases in Childhood

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Life-style related diseases such as strokes and heart disease account for over 60% of total deaths and comprise Japan's greatest health problems. The primary, secondary, and tertiary prevention measures, development of treatment systems and fostering of experts have actively been promoted by the Japanese government. Recently it has been proposed that the high occurrence of life-style related diseases such as hypertension, high cholesterol, arteriosclerosis, and diabetes are causing expectant mothers to worry. This is turn is causing babies in the womb to become malnourished and resulting in a higher number of low birth weight infants.

Blood pressure, obesity, serum levels of total cholesterol, high-density lipoprotein cholesterol, and triglyceride are identified as risk factors for coronary heart disease. During the last 30 years these risk factors were found not only in adult age groups, but also in the younger generation. It is clear that these conditions occurred due to the individual's life-style and poor eating habits over many years. Thus, the prevention of these diseases is essential from an early age. Education and nutritional assessment are necessary to eliminate these risk factors and are now being emphasized for young people. However school based intervention trials have not been conducted throughout the country.

This report looks investigates the intervention trials that were started at the community level in 1984 and have been continued for the past 25 years. The trials were conducted on children between the ages of 4-5, 9-10 and 12-13 who were living in the suburbs of a metropolitan area.

The study consisted of physical and biochemical tests such as anthropometrical measurement, obesity, serum levels of cholesterol, HDL cholesterol, triglyceride, blood pressure and hemoglobin. At the same time daily activities, food frequency and 24 hour-recall dietary intake were investigated. From these data the relationship between food intake, life-style and daily activities were investigated. The bodyweight of the participants was taken at birth to investigate the relationship between low body weight at birth and risk factors that followed when they grew up. The influence of a low birth weight was found in cholesterol levels for children aged 4-5 and 8-9. However, influences at the 12-13 year old age range were not found.

Counseling on nutrition and daily activities was given to children who were identified as having risk factors. Furthermore, nursery schools, primary schools and junior highs were visited to give special nutritional education sessions every year. Results indicate that nutritional education and individual counseling are effective methods for improving these risk factors. The incidence rate of risk factors has been decreasing from 46% in 1983 to 29% in 2004. Therefore long time nutritional education support will be very effective in reducing risk factors and their food behavior changes.

セッションⅡ-2

妊娠期の低栄養の現状

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要旨：妊娠期の低栄養の現状

2003年のわが国の周産期死亡率・乳児死亡率はそれぞれ出生1,000対5.3と3.0であり、世界で有数の低値である。しかし、わが国はOECD加盟国中最も低出生体重児割合が高い。

そこで、妊娠期の女性の健康に関する問題点を明らかにする目的で 1) 国民栄養調査を用いた分析 2) 乳幼児発育調査を用いた分析 3) 妊娠初期～末期の妊婦を対象とした食事調査・血中栄養指標と妊娠転帰に関する分析を行った。

対象と方法

1) 国民栄養調査データから、1995-99年の妊婦330名と、年齢・調査年および地域・血液検査の有無で1対1マッチングさせた非妊婦（対照群）のデータを用いて、栄養素摂取量や生活習慣、貧血の状況について比較を行った。
2) 厚生労働省が10年に1回実施している乳幼児発育調査データから1980，1990，2000年の3時点の一般調査のデータを用い、出生時身体発育値の変化とその関連因子について検討を行った。
3) 東京都の2施設の妊婦94名に対し、妊娠初期・中期・末期の各時点における栄養素等摂取量と血中栄養指標（葉酸・ビタミンB_{12}・総ホモシステイン）と出生児の身体発育指標との関連を解析した。

成績

1) 妊婦群と対照群ではエネルギー摂取量に有意差が見られなかった。妊婦群は対照群に比べ炭水化物、カルシウム、ビタミンB_2の摂取量が有意に高かった（$p<0.05$）。しかし、食事からの平均鉄摂取量は妊婦群で11.0 ± 4.6 mg/日、対照群で10.6 ± 4.5 mg/日と低かった。
2) 1980年の平均出生体重は3,18 ± 422 g、1990年は3,123 ± 421 g、2000年は3,033 ± 429 g と減少傾向にあった。また、1990年から2000年にかけて母体の妊娠中喫煙率が6.5%から10.9％へと有意に増加しており、とくに20歳代における喫煙率の増加が著しかった。
3) 妊娠期を通して1日の平均エネルギー摂取量は約1,800kcal、葉酸摂取量300μgを下回った。血中葉酸とビタミンB_{12}は妊娠の進行とともに低下傾向にあり、総ホモシステイン値は中期から末期にかけて上昇した。妊娠末期の総ホモシステイン値が高い者で児の出生体重が低い傾向が見られた。

結論

国民栄養調査と乳幼児発育調査の結果から、妊娠中の栄養摂取が十分でないことや喫煙率が上昇していることが明らかとなった。また妊娠期を通じた調査から、胎児発育に不可欠な栄養素の不足と、胎児発育への影響が示唆された。

SESSION II -2

Undernutrition during Pregnancy in Japan and Proposals for Its Improvement

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Infant mortality rate in Japan is one of the lowest in the world. On the other hand, the proportion of low birthweight (LBW) infants is rising, being the highest in OECD countries.

In order to investigate the background of the increase in LBW infants, we analyzed the current nutritional status of pregnant women, by using the National Nutrition Survey and the Children and Infant Growth Survey data. We also conducted a dietary survey and

Methods

1) Three hundred thirty pregnant women their non-pregnant controls were selected from the 1995-99 National Nutrition Survey data for the analyses of dietary intakes and blood biomarkers.
2) The 1980, 1990, and 2000 Children and Infants Growth Survey data was used to identify the relationship between infant anthropometry and maternal factors.
3) Ninety-four pregnant women were followed up from the first trimester to birth, and their dietary intakes, blood biomarkers and infant anthropometry was assessed.

Results

1) There was no significant difference in energy and iron intakes between pregnant women and their controls. However, the intakes of carbohydrates, calcium, and vitamin B_2 were significantly higher in pregnant women than controls.
2) Mean birthweight decreased from 3,189 ± 422g in 1980 to 3,123 ± 421g in 1990, and to 3,033 ± 429g in 2000. Maternal smoking rate increased from 6.5% in 1990 to 10.9% in 2000.
3) Mean energy intakes throughout pregnancy were approximately 1,800kcal, and folate intakes were less than 300μg per day. Serum folate and vitamin B_{12} concentrations decreased as pregnancy progressed, and plasma total homocysteine concentrations increased. Infants born to women with elevated plasma total homocysteine concentrations had lower birthweight.

Conclusion

The results form the two national surveys demonstrated that overall dietary intake in pregnant women were insufficient, and maternal smoking rates were increasing. Results from the longitudinal pregnancy survey suggest that nutrient intakes are insufficient to promote adequate fetal growth in Japanese women.

セッションⅡ

セッションⅡ-3

胎生期の栄養環境と成長後における肥満発症

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我が国では全て日世代の成人男性ならびに40代以降の女性のBMIは過去50年間一貫し増加し肥満が増加している[1]。しかし、20代、30代といった妊孕世代女性のBMIは逆に急激に減少している[1]。若年女性のやせが増加する現象には、やせ願望による不自然なダイエットなどが影響を及ぼしていると考えられている。興味深いことに、1970年をピークに、国民1人あたりの総摂取エネルギーは減少の一途をたどっている[1]。総摂取エネルギーが減少しているのに肥満が増加する原因は必ずしも明らかではないが、非都市部における車社会の浸透などによる運動不足などの関与が指摘されているが、必ずしも明らかではない。

一方、我が国では正期産児の出生体重が減少していることから、若年女性の不自然な食生活あるいは喫煙率の増加などが胎生期の栄養環境に何らかの影響を及ぼしている可能性が危惧されている。

近年、胎生期に低栄養環境に曝されると、恒久的な省エネルギー体質を獲得するというthrifty phenotype hypothesis（倹約表現型仮説）が提唱されている[2]。thrifty phenotypeを獲得すると出生後の饑餓環境には良好に適応するが、現代のような飽食の時代を生きた場合に適応不全をきたして肥満や2型糖尿発症のハイリスクとなると想定されている。残念ながらthrifty phenotypeの科学的なメカニズムは充分に解明にされていない。

本研究では、妊婦の栄養摂取不足が次世代においてthrifty phenotypeを増加させ、肥満発症率増加の少なくとも一部に関与している可能性を想定して、マウス母獣の摂餌制限による胎生期低栄養モデルを用いてthrifty phenotype獲得機序の一端の解析を試みた。

妊娠マウスの妊娠後半期に30%の摂餌制限を加え、出生した仔（8～16週齢）に高脂肪餌を与えたところ、胎生期の低栄養群では正常対照群対して、有意に肥満が増悪した（脂肪蓄積量で30～40%増加）。ミトコンドリアにおける熱産生すなわちdiet induced thermogenesis（DIT）は脂肪蓄積の制御において重要な役割を果たすことが知られている。このマウスモデルを解析したところ、高脂肪餌負荷に対してDITの上昇反応が低下していることが明らかとなりthrifty phenotypeの獲得機序に関与する可能性が示唆された[3]。胎生期に低栄養状態にあったマウス新生仔にmonosodium glutamateを投与することで、視床下部の弓状核を化学的に障害したところ、高脂肪食負荷に対する肥満の増悪を改善することができたことから、胎生期の低栄養環境に起因する肥満の増悪には視床下部の弓状核が重要な役割を果たしている可能性が示唆された。そこで、視床下部の弓状核と室傍核においてにおいてエネルギー代謝や摂食に関与する神経ニューロンを検討したところ、pro-opiomelanocortin（POMC）神経繊維には変化を認めなかったが、Nneuropeptide Y（NPY）ならびにcocaine and amphetamine-regulated transcript（CART）の神経繊維の発達が亢進し、エネルギー代謝調節の神経回路の構造に何らかの変化が認められる可能性が示唆された。さらに、視床下部において抗肥満ホルモンであるレプチンに対する感受性が低下していることが明らかとなった。

以上の検討から、胎生期の低栄養環境に起因するthrifty phenotypeの獲得、とりわけ高脂肪餌負荷に対する易肥満性とも言うべき形質の獲得に関して、視床下部の弓状核を中心とするエネルギー代謝調節に関わる神経回路の変化が重要な役割を果たしている可能性が明らかとなった。また、その一端には中枢性の低レプチン感受性の獲得が関与している可能性が示唆された。

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SESSION II -3

Intrauterine Undernutrition and Adult Obesity

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In these five decades, obesity has gradually increased and is now a public health problem in Japan. However, as for the mean body mass index (BMI) of the young women of child-bearing age such as 20 and 30 year old generations, it has constantly decreased, probably due to prevalence of inappropriate diet. Interestingly, the entire energy intake per a person has gradually decreased after 1970. At present it is yet to be fully clarified why obesity has increased while energy intake has decreased in modern Japanese people, although a possible association of a tendency of lack of physical activity especially in the non-urban district, where people mostly use cars instead of walking.

On the other hand, the mean birth weight of Japanese term newborns has gradually and steadily decreased. It is suggested that inappropriate dietary life of the Japanese young women may, at least partly, be associated with a tendency of decrease in birth weight.

In 2001, Hales and Barker proposed the novel concept of thrifty phenotype hypothesis that undernourished fetuses may permanently develop a phenotype of high efficient energy expenditure, which is supposed to adapt well to the later life of expected insufficient food supply (*Br Med Bull* 60; 5-20, 2001). If the neonates of thrifty phenotype experience cafeteria diet in modern times, the acquired high efficiency in energy expenditure is hypothesized to predispose themselves to obesity and/or type 2 diabetes mellitus in later life. It is plausible that a possible development of thrifty phenotype might be causatively associated with a prevalence of adult obesity concomitant with rather small newborns in recent Japanese people, although no direct evidences are available at present to prove this speculation.

To investigate the mechanism of developing thrifty phenotype, we prepared a mice animal model of undernutrition *in utero* by maternal food restriction of 30% in the latter half of pregnancy, which offspring showed significant exacerbation of obesity on high fat diet in the adult period. Using this animal model, we revealed that undernutrition *in utero* programs permanent low sensitivity in augmentation of mitochondrial diet induced thermogenesis (DIT) in response to high fat diet, which is at least partly involved in the acceleration of obesity under high fat diet, presumably as a mechanism of developmental origins of obesity. We subsequently demonstrated that the changes of hypothalamic regulatory system in energy expenditure is associated with the development of low DIT responses, i.e. hypothalamic low sensitivity against circulating leptin, an adipocyte-derived satiety peptide, as well as structural changes in neural circuit in hypothalamic arcuate nucleus (ARH), assessed by the density of nerve terminals containing neuropeptide Y (NPY) or cocaine and amphetamine-regulated transcript (CART).

In conclusion, the present study suggests that undernutrition *in utero* permanently causes structural and functional changes in hypothalamic regulatory system of energy expenditure, which may be at least partly involved in the development of thrifty phenotype, as a mechanism of developmental origins of obesity.

セッションⅡ-4

胎児期を含めた、生活習慣病に関する栄養プログラミング

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SESSION II -4

Nutritional Programming of Adult Disease

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セッションⅢ-1

高齢者の食事と生活習慣病

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生活習慣病という名称が示すとおり、高齢者においては、高齢期の生活習慣が疾病の原因になるというよりは、それまでの生活習慣が高齢期の疾病の発症を左右しているとみるべきだろう。つまり、高齢期の疾病、特に、生活習慣病の発症を予防したいと考えれば、高齢期の生活習慣をどのように改善するか、ではなく、高齢期までの生活習慣をどのように改善するかが重要であることがわかる。

たとえば、高齢者で大きな健康問題のひとつである高血圧を例にあげ、ナトリウムの過剰摂取との関連を考えると、ナトリウム摂取量（または24時間尿中ナトリウム排泄量）と血圧とのあいだには目立った関連は観察されていない。一方、ナトリウム摂取量（または24時間尿中ナトリウム排泄量）と加齢による血圧上昇量とのあいだには有意な正な関連が観察されている。Intersalt Studyの結果から類推すると、食塩1g/日の減塩で抑制できる年間収縮期血圧上昇量は0.0058mmHgとなる。微々たるものと感じられるかもしれないが、14g/日の食塩を習慣的に摂取している20歳の人が9g/日に改善すれば、70歳のときに期待される血圧上昇抑制量は、0.0058×（14－9）×（70－20）＝14.5mmHgである。もしも150mmHgになるはずの人であれば、135.5mmHgに抑えることができることになる。一方、1か月間の減塩で下がる血圧はおよそ1mmHg/1g減塩であり、1か月間以上継続しても下げ止まりの傾向があるため、短期間（たとえば1年以内）に14.5mmHgもの血圧を減塩だけで下げるのは無理である。この試算から、高齢になってからの生活改善よりも、高齢期までの生活習慣の重要さが理解される。

では、高齢者にとって必要な栄養とは何か。高齢の日系ハワイ人を追跡した結果によると、肥満度（BMI）と皮下脂肪厚は総死亡率に有意な負の関連を示している。これは中年層で観察されるJ字型とは異なる結果である。この結果は、高齢者では、肥満、または、脂肪の蓄積が必ずしも死亡率を高めるものではないことを示している。

上記、2つの代表的な研究から学ぶべきことは、個々の生活習慣病の危険因子や予防因子となる栄養素については高齢化以前の生活習慣が重要であり、高齢者においては、ある程度の脂肪や筋肉の蓄積など、いわゆる体力に資する要因が重要であることを示しているものと理解される。この考えは、やせ群の死因に呼吸器感染症が多く、これはいわゆる体力に帰する問題のように思われることに符合する。

一方、高齢者に特異的でQOLの低下の大きな原因となるものは認知機能低下であろう。認知機能低下に関連する栄養素について、近年、精力的な研究が国外では行なわれており、かなりのエビデンスが蓄積されてきた。しかしながら、結果は研究によって異なり、まだ結論は得られていない。その中では、高葉酸摂取、高n－3系脂肪酸摂取によって認知機能低下が抑制される可能性が複数の研究によって報告されている。ともに、欧米人に比べて日本人で摂取量が多い栄養素であるため、ぜひ、日本からエビデンスを出したいものである。

以上のように、高齢者の生活習慣病の原因は、現在というよりも過去の生活習慣に負うところが大きい。一方、栄養、特にマクロ栄養素は、体力の基礎を支えるものである。栄養におけるこの二面性に注意し、高齢者の健康に資するエビデンスを構築しなければならない。

SESSION Ⅲ-1

Diet and Lifestyle-related Diseases in the Elderly

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As indicated by its name, lifestyle-related diseases, dietary habits until the elderly cause lifestyle-related diseases later in life, rather than dietary habits in the elderly cause lifestyle-related diseases in the elderly. Therefore, in order to prevent lifestyle-related diseases in the elderly, how to manage (modify) dietary habits until the elderly is more important than how to manage (modify) dietary habits in the elderly.

Let's take salt intake and hypertension as an example. We do not find strong significant relationship between salt intake (or the 24-hour urinary excretion) and blood pressure. On the other hand, at a population level, salt intake (or the 24-hour urinary excretion) significantly correlates to the rise of blood pressure by aging per year. The Intersalt Study allows us the estimation of this rise: reduction of blood pressure rise by aging per year by 1g/day salt reduction is around 0.0058mmHg. Although it looks small value, it is quite a big. If a 20-year old person with 14g/day salt intake reduces the intake by 5 g/day, the expected reduction of blood pressure rise by aging at age of 70 years is about 14.5mmHg. This estimation shows the importance of life-long maintenance of desirable dietary habits rather than modification of diets in the elderly.

Next, what are the important nutrients in the elderly? A cohort study held in Hawaii for elderly Hawaiians with Japanese origin showed a negative association between body mass index (BMI) and skinfold thickness and all-cause mortality. This is different from the results obtained from the middle-aged populations: the J-shaped curve. This result indicates that obesity or adiposity do not necessarily increase mortality in the elderly.

We learn the following from the above-mentioned two studies. Dietary habits before the elderly is more important for nutrients related to each lifestyle-related disease. In the elderly, some factors related to physical strength such as accumulation of adipose tissue and muscle until a certain level is important. This idea is partly supported by the fact that mortality from circulatory infectious disease is more common in lean populations than in obese counterparts.

On the other hand, one of the biggest problems against QOL in the elderly is probably lowering cognitive function. Several epidemiologic studies have recently reported the association between nutrient intakes or biomarkers of dietary intake of specific nutrients and cognitive function. However, the results are not necessarily consistent. Among them, more than one research reported a beneficial effect of high intakes of folate and n-3 fatty acid. Because the intake is relative high in both nutrients in Japanese compared to Westerners, more evidence is waited in this issue from Japanese studies.

In conclusion, the causes of lifestyle-related diseases in the elderly attribute to the past lifestyle rather than the current ones. On the other hand, macro-nutrients are nutrients which support physical strength in the elderly. Considering these two aspects of nutrients, we should establish more evidence for health of the elderly.

セッションⅢ-2

慢性閉塞性肺疾患（COPD）患者における栄養療法と運動療法の有用性

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1. はじめに

慢性閉塞性肺疾患（chronic obstructive pulmonary disease; COPD）とは、肺気腫、慢性気管支炎または両者の併発により引き起こされる閉塞性換気障害を特徴とする疾患である。近年、COPDが増加している背景として、COPDの最大のリスク因子であるタバコ喫煙が先進工業国のみならず発展途上国においても高率となっている。また本症が好発する高齢者が急増している社会状況がある。このため、COPDの有病率、死亡率、社会経済的負担は全世界的に増加し、このまま増加すれば、COPDは2020年には全世界の死亡原因の第3位になると予測され、COPDの治療・ケアおよびその発症予防が急務の課題である。

2. 栄養療法

中等症以上のCOPDの約25%、最重症COPDの約40～50%に%IBW（%標準体重）90%未満の体重減少がみられる。体重減少を認めるCOPD患者は、呼吸不全の悪化や累積死亡率が高く、体重減少は気流閉塞とは独立した予後因子とみなされている。COPDの栄養障害の機序としては、従来から、1)エネルギー消費量の増加すなわち代謝亢進、2)カロリー摂取量の低下が報告されている。カロリー摂取量の原因としては、食事中の動脈血酸素分圧の低下、抑うつ状態による心理的影響、胃潰瘍など消化器疾患の合併などが考えられている。近年、COPDはtumor necrosis factor-α（TNF-α）、可溶性TNF-α、IL-8などの炎症性サイトカインや種々のホルモンを介したsystemic inflammationと考えられている。

食事摂取量を増やすことが困難な場合や中等度以上に%IBWの低下を示す場合に栄養補給法が考慮される、実測REEの1.5～1.7倍のエネルギー摂取を目標にして栄養補給を行う。栄養補給療法単独の効果に関しては、無作為比較対照試験のメタアナリシスでは十分な証拠は確認されていない。

しかし、近年、多価不飽和脂肪酸を多く含む栄養補助食品摂取の有用性、分岐鎖アミノ酸の併用効果、コエンザイムQ10含有補助食品の有用性などが報告され、栄養療法に再び注目が集まっている。COPD患者の栄養管理にあたっては個々の患者について、簡易カロリー計を用い安静時エネルギー代謝を測定し、個人個人の安静時エネルギー代謝に応じて長期にわたる栄養管理を行うことが重要である。

3. 運動療法

運動療法は呼吸リハビリテーションの中核となる構成要素である。在宅で実際に運動を行う場合には、現在、その簡便さ、リスクの低さなどから、歩行がよい。歩行の処方は、トレッドミル、エルゴメータによる運動負荷試験や、フィールド歩行テストによる最大酸素摂取量の測定あるいは推測を行って、運動強度を決める。しかし、このような運動強度の設定は、日常診療が多忙すぎる医療現場では実施が不可能なことが多い。Mahlerらは、こうした歩行スピードの体得は難しいので、呼吸困難を指標に運動強度を決定する運動療法（TDR;Target Dyspnea Rating）を推奨している。最近、我々はより低いTDRで行う低強度運動療法である、「椅子に座って行う体操」の有用性を報告している。

従来、下肢筋トレーニングに対しては重錘などを足首に巻いて下肢の伸展屈曲を行う方法が主として行われてきたがその効果は不十分であった。最近、佐藤らは、自身の体重をサポートするトレーニングマシーン（MUSTEC®）を考案し、下肢筋をスクワット運動によりトレーニングし効果をあげ注目されている。

近年、推奨されているhigh-intensityプログラムでは実施回数が少ないlow-frequencyとならざるを得ず、結果として効果が小さくなるという現状がある。さらに、最近在宅における運動療法プログラムの実施率は、実際はさらに低くなることを考慮すると、継続性を重視した運動強度を低く実施頻度を多くした低頻度高強度（low-intensity high-frequency）運動療法プログラムが理想的であり、実際、このようなプログラムの有用性が報告されてきている。

SESSION Ⅲ-2

Effectiveness of Nutritional Support and Exercise Training in Patients with Stable COPD

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1. Introduction

Chronic obstructive pulmonary disease (COPD), which features the characteristic airway obstruction which is composed by emphysema and chronic bronchitis or the concurrence of both. As for the background of increasing of COPD, two major reasons have been pointed out. First, the rate of tobacco smoking that is the largest risk factor of COPD is increasing in not only advanced industrialized country also in the developing country. Second, the number of the aged person who suffers from COPD is increasing in the whole world. Because of increasing of the morbidity and mortality rate of COPD, social economic burden increases in the entire world. If COPD increases as it is now, it is forecasted that it will reach to 3rd rank of the cause of death in the world by 2020. Thus the new system for remedy, care and prevention system in COPD is urgent.

2. Nutritional support therapy

The weight loss under 90% of ideal body weight (IBW) was seen in approximately 25% of COPD in the stage II (moderate) of COPD, 40-50 % in the stage IV (very severe) of COPD, respectively. Cumulative mortality rate is so high in COPD patients who recognize weight loss, or deterioration of respiratory failure that weight loss is considered to be the risk factor that is independent from airway obstruction. As for the mechanism of the nutritional disturbance of COPD, 1) increased metabolism of the energy consumption, 2) decrease of the caloric intake have been reported from the past. As a cause of loss of the caloric intake, decrease of blood oxygen tension during the meal, psychological influence such as depression and the digestive organs disease such as gastric ulcer have been reported.

Recently, COPD is considered to be a systematic inflammatory disease due to inflammatory cytokine such as TNF-α, soluble TNF-α, and IL-8 or other hormones. When it is difficult to increase quantity of the meal intake in COPD patient whose body weight is below 90% of IBW, nutritional support is considered. Nutrition support is done with the energy intake of 1.5 - 1.7 times high resting energy expenditure (REE) than usual REE that is actually measured in the patient as a target. There have been no established evidences in nutrition support therapy in the meta-analysis so far. However, recently, usefulness of the nutrition support with food that contains the polyunsaturated fatty acid, branched-chain amino acid and coenzyme Q_{10} has been reported, and attention has focused on nutrition supplement therapy again. In the nutritional management of the COPD patient it is important to support nutrition according to the individual REE using the simple caloric meter which has been developed recently.

3. Exercise therapy

Exercise therapy is the core component of pulmonary rehabilitation. When patient exercises at home, walking is recommended as for its simplicity and low risk. Prescription of walking is done according to the intensity which is decided from the exercise test such as treadmill, cycle ergometer and field walking test. But, decision of the exact intensity is difficult in daily busy medical care field. Mahler has reported effectiveness of Target Dyspnea Rating (TDR) in which walking speed is decided according to dyspnea during walking in 2004. Recently, we devised low intensity chair exercise which is done with lower TDR.

Until recently, lower extremity exercise training was done winding the weight around the ankles, but the effect of this exercise was insufficient. Recently, Sato developed the new training machine (MUSTEC™) which supports own weight when they bend their legs muscle with squat motion and the effectviness of this machine has been reported. Until very recently, the high-intensity program has been recommended, but it becomes low-frequency program and effect is small. Furthermore, the execution ratio of high-intensity exercise training is usually low at home. From these facts, low-intensity and high frequency exercise training is ideal and effectiveness of this type of exercise program has been recognized.

セッションⅢ-3

高齢者の免疫能を強化するための栄養学的戦略

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世界的に人口構造が変化し、高齢者人口比率の著しい増加が見られる。経済的、社会的重要性が高いにもかかわらず、高齢者層の脆弱な免疫状態を改善する試みは、ほとんどなされていない。現在のところ、「免疫老化」とも呼ばれている免疫機構に及ぼす加齢の影響は、先天性の適応的免疫機能が加齢に伴い調節不全になった状態、と定義されている。免疫老化は、伝染病、自己免疫疾患、癌などの罹患率および死亡率の増加の原因となっている。炎症状態の亢進（軽度の慢性炎症）に関する科学的エビデンスが蓄積されつつあるが、この慢性炎症が加齢に伴う免疫調節不全に関与している可能性が高い。内因性で、真に年齢依存的な変化は、有害な環境要因によりさらに悪化すると思われる。この年齢依存的な変化により損なわれた免疫機能の一部は、栄養学的介入によって改善されることが示された。

数例の栄養学的介入研究では、高齢者の免疫機能を調節できる可能性が高いことが示された。ビタミンEやグルタチオンなどの抗酸化物質、ないしは、マルチビタミンやミネラルの混合物、特に亜鉛やセレンを食事補給すると、高齢マウスやヒトの免疫機能を向上させることが示された。免疫賦活作用のあるプロバイオティクス乳酸菌の摂取も、高齢者にとって有効であることが示唆されている。菌株の中には、顆粒球の貪食やNK細胞の活動を増強することが明らかとなったものもあり、感染症の発生率低下が期待できる。n-3多価不飽和脂肪酸や共役リノール酸などの脂質も、一部の免疫特性を活性化すると報告されているが、副作用を伴う可能性が示唆されている。

本報告では、炎症を抑え、高齢者の免疫機能を回復する為の、現在の栄養学的戦略並びに革新的概念について述べる。

SESSION Ⅲ-3

Decline of Immune Function in the Elderly and Recovery by Nutrition

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A demographic change is observed worldwide leading to considerable increase in the proportion of the elderly population. Although this group is of high economic and social importance, little has yet been done to ameliorate its vulnerable immune status. The influence of ageing on the immune system, also called 'immunosenescence', is currently defined as the state of age-associated dysregulation of the innate and adaptive immune function that contributes to morbidity and mortality due to increased incidence of infectious and autoimmune disease as well as cancer. Scientific evidence on the increased inflammatory status (chronic low grade inflammation) has been accumulated, most likely contributing to the immune dysregulation with age. Intrinsic, truly age-dependent changes are presumably further exacerbated by detrimental environmental factors. Influencing the latter by nutritional intervention has been shown to improve some features of impaired immunity.

Some nutritional interventions have demonstrated promising potential in modulating immune functions in the elderly. Dietary supplementation with antioxidants, such as vitamin E and glutathione, or multivitamin and mineral mixtures, especially zinc and selenium, have been shown to improve immune function in aged mice and humans. Elderly may also benefit from the consumption of immunostimulatory probiotics. Some strains were shown to enhance phagocytosis of granulocytes and NK cell activity and may therefore alleviate the incidence of infections. Lipids , such as n-3-PUFA or conjugated linoleic acid (CLA) are also reported to stimulate some immune features but may also display adverse effects.

The current paper will discuss current nutritional strategies and new innovative concepts to counteract inflammation and restore immune function in the elderly.

セッションⅢ-4

自立高齢者の老化遅延のための食生活

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高齢者の健康問題は、加齢に伴う身体機能低下と深く連関している。したがって、高齢者のヘルスプロモーションプログラムのターゲット、「老化そのもの」である。先行研究は血清アルブミンの低いことが生活機能低下を促すことを示している。さらに、骨格筋肉量や歩行速度の加齢低下は血清アルブミン値により独立的に規定されており、この関係は臨床医学的には正常域とされる38g/L以上においても認められる。高齢者では、栄養状態がノーマルレンジであってもより水準の低い者ほど老化が加速されやすい。高齢者への栄養介入では、可能な限り身体栄養状態を高める手立てが求められる。地域高齢者の大規模集団を対象とした介入研究で栄養改善の有効性が実証できた食生活ガイドラインは以下のとおりである

1）欠食は絶対さける
2）動物性たんぱく質を十分に摂取する
3）魚と肉の摂取は１：１程度の割合にする
4）油脂類の摂取が不足しないように注意する
5）牛乳を毎日200ｍl程度飲む
6）健康情報を積極的に取り入れる
7）会食の機会をつくる

疾病とは本質的に異なる普遍的、かつ連続的変化である「老化」を目的変数にした縦断研究と介入研究の成果は、本来実践すべき「食の多様性の維持増進」の重要性を教えている。生活習慣病をはじめとした個別疾病のリスクファクターを探索する研究では検出しえない食の本質が垣間みえる。

SESSION Ⅲ-4

Dietary Habits to Postpone Aging Itself in Old Age

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The health problems of the elderly people are associated with physical functional decline based on aging substantially. Therefore, the targets of health promotion programs for the elderly people are to postpone aging *per se*. Previous studies showed that low serum albumin level significantly accelerated future functional decline with advancing aging. Furthermore, Lower serum albumin concentrations, even above the clinical cutoff of 38g/L are independently associated with future decline of skeletal muscle mass and maximum walking speed in functionally competent older persons. Lower nutritional status, even in clinical normal range may be a risk factor for advancing aging. On the nutritional intervention for the older persons, the means to enhance nutritional status as much as possible are required. The effective dietary guidelines of nutritional improvement based on the intervention study of the functionally competent community-living elderly people are as follows:

1) Avoid skipping a meal.
2) Eat adequate amounts of animal protein.
3) Eat equal amounts of meat and fish and shellfish daily.
4) Eat adequate amounts of various fats and oils.
5) Drink a cup of milk (200ml) daily.
6) Have an interest in obtaining health information.
7) Take a meal together with a companion.

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P-1

Amino Acids Modulate Erythropoiesis in Aged Mice

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Numerous studies over the past decade have compared the changes in gene expression in various tissues of aged animals to the same tissues of young animals in order to understand how genes relate to aging. As a result, a large number of genes associated with aging have been discovered. However, the effects of the change in these genes on homeostasis and the mechanism by which this occurs remain unclear. Our laboratory has studied aging and the effects of ingestion of various nutrients on aging using naturally aged mice. In the process, we found that the hemoglobin concentration in older mice (24 months old) was lower than that of young mice (1 month old). The same changes have been reported in humans, so it is assumed that aging reduces erythropoiesis in hematopoietic tissue. It is now understood that amino acids are not only macronutrients but that they also exhibit many physiological functions. We gave amino acids to 24-month-old mice for two months and found that ingestion of amino acids prevented reduction in blood hemoglobin levels in the aged mice. Furthermore, using spleen, hematopoietic tissue in mice, the gene expression patterns were analysed using a DNA micro array and the results of young mice (1.5 and 9 months old) and old mice (28 months old) were compared. We used an Affymetrix MOE 430A array containing probe sets for approximately 22,000 mouse genes for this analysis. Four mice from each experimental group were used for the GeneChip analysis. We found that several genes related to erythropoiesis, e.g. heme biosynthesis, structural proteins of red blood cells and erythroid-specific differentiation markers etc., were down-regulated in the old mice, but recovered to the same level as young mice following administration of amino acid mixtures containing essential amino acids. Moreover, hierarchical clustering analysis of the hematopoietic related genes revealed that the results for aged mice group given the amino acid mixture were much more similar to the results for the young group than to the results for the control aged mice group. In conclusion, these results suggest that amino acids modulate erythropoiesis and inhibit the age-related decrease in activity of hematopoietic stem cells.

POSTERSESSION

P-2

Effects of Agar on the Glucose Release from the Cooke Rice

Hatsue Moritaka, Yukiko Nakanishi, Atsuko Sagawa, Mami Takahashi, Shuichi Kimura

Showa Women's University

The effects of agar on the glucose release from the cooked rice were discussed by the sensory evaluation and the measurements of the hardness and the blood sugar level. The concentrations of agar (San Ei Gen F.F.I Corp., Osaka) were 1.0, 1.7 and 2.5% for the rice weight (Koshiibuki harvested in Niigata Prefecture in 2006). The volunteers for measurement of blood sugar level and the sensory evaluation were consisted of Showa Women's University students who had a normal fasted-blood sugar level and normal sensations of taste, hearing and seeing. The thermal property was measured by Micro-DSC III (Setaramu, France).

Hardness of the cooked rice with agar did not associate with the concentration of agar. From the results of sensory evaluation for "appearance", "flavor", "taste", "adhesiveness", "hardness" and "all over evaluation" of the cooked rice with agar, all of those evaluations decreased with increasing agar concentration ($p<0.05$). The blood sugar level and Glysemic Index value of the cooked rice significantly decreased by addition of 1.0% agar compare to cooked rice without agar and then decreased more by more than 1.0% agar. Although the enthalpy of rice grain with agar was bigger than that of the rice grain and that of agar, the enthalpy of rice grain with agar was smaller than the total amount of enthalpies of rice grain and agar. From these results, the inhibition of glucose release from the cooked rice with agar may be due to the suppression of the swelling and the hydration of rice grains and of the absorption of the released glucose by agar molecules as a dietary fiber.

P-3

Relationship between Rheological and Swallowing Properties of Solid-dispersed Sol

Atsuko Sagawa, Mariko Morishita and Hatsue Moritaka

Showa Women's University

An investigation was made on rheological properties and swallowing ones of 4 agar gel samples, which were dispersed in xanthum gum, guar gum, starch sol and water. The former three sols were made of different raw materials. Texture and dynamic elasticity were chosen as a measurement for rheological evaluation, whereas for subjective evaluation, sensory evaluation was made by 5-rating method. Flow rate of food mass in these agar samples was determined using ultrasonography under two conditions of 5 time chewing and 30 time chewing.

It was demonstrated that the hardness of xanthum-dispersed agar sample was lowest and its cohesiveness was highest among these samples and none of its rheological properties, swallowing ones and maximum flow rate was affected by the mixing ratio of sol or the times of chewing.

Whereas for guar gum-dispersed agar sample, the hardness and G' were decreased as increasing the times of chewing, but its maximum flow rate was increased as increasing the times of chewing.

The hardness of starch agar gel sample and its G' were decreased as increasing the times of chewing, but the maximum flow rate was raised.

On the other hand, the maximum flow rate of food mass in the water-dispersed agar sample and the hardness were both highest among these samples even after chewing. When the mixing ratio of sol is raised, the sensory evaluation indicated that a feeling of softness became significantly more marked by increasing the mixing ratio for either of these sols.

The degree of easiness for swallowing was not influenced by either of mixing ratio for xanthum and guar gum, i.e., there was no difference in the degree of easiness for swallowing between xanthum gum and guar gum.

From these findings, it was concluded that xanthum sol was most appropriate as a thickening agent because its rheological and swallowing properties were less affected by the times of chewing and sol mixing ratio.

POSTERSESSION

P-4

Relationship between Consumed Food and Death Rates for Lifestyle-related Diseases in Each Prefecture of Japan

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*Graduate School of Health Science, Hiroshima University

In Japan, the aging of the population has raised issues regarding not only the longevity of individuals, but also maintenance of a high quality of life (QOL) in old age. Therefore, the present study focused on lifestyle-related diseases, which cause death in late middle age, shorten healthy life expectancy, and reduce QOL. In addition, we examined diet, which is thought to be related to lifestyle-related diseases. Relationships between consumed food and the death rates for lifestyle-related diseases in each prefecture were investigated with the objective of realizing healthier diets.

The death rate for lifestyle-related diseases was given as the sum of death rates for malignant neoplasms, heart disease, cerebrovascular disease, diabetes, and hypertensive disease from the Age-adjusted Death Rates by Prefecture in 2000. Information regarding consumed food was taken from data from the National Survey of Family Income and Expenditure conducted in 1974, 1979, 1984, 1989, 1994, and 1999. A multiple regression analysis was performed using the death rate for lifestyle-related diseases as the dependent variable and the food consumed each year as the explanatory variable. In addition, factor analysis was performed in order to obtain a comprehensive understanding of the death rates for lifestyle-related diseases and consumed food that were investigated in the present study.

The death rate for lifestyle-related diseases among men was higher for those consuming large amounts of seafood, beverages, and alcoholic beverages and small amounts of cooked food. Among women, the death rate for lifestyle-related diseases was higher for those consuming large amounts of vegetables, potatoes, beans, mushrooms, seaweed, and snacks. Factor analysis revealed the following six factors: first factor, consumption of cooked food differed from that of other food; second factor, the death rates for cerebrovascular disease among men and women were related to consumption of meat; third factor, the death rates for heart disease among men and women were similar to the death rates for diabetes and malignant neoplasms among women; fourth factor, the death rate for malignant neoplasms among men was related to consumption of alcoholic beverages; fifth factor, the death rate for diabetes among men was related to consumption of beverages; and sixth factor, consumption of vegetables, potatoes, beans, mushrooms, and seaweed differed from other consumed food and the death rate for lifestyle-related diseases.

Considering that the data represent the mean values for 47 prefectures, and that specific details regarding the consumed food and cooking methods were not known, further study involving surveys at the individual level is desired.

POSTER SESSION

P-5

Palatinose (Isomaltulose) and Xylitol, in the Newly Designed Low Glycemic Enteral Formula Inslow, Act to Reduce the Accumulation of Visceral Fat in Mice

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POSTERSESSION

Inslow, a newly designed low glycemic enteral formula, was shown to prevent the accumulation of visceral and subcutaneous fat in our previous study. The disaccharide palatinose (isomaltulose), α-1, 6-linked glucose and fructose, is one of the major components of carbohydrates in Inslow. Because palatinose is fully absorbed in the intestine after gradual digestion by isomaltase and thus inhibits postprandial hyperglycemia, we thought that palatinose acted to reduce fat accumulation. However, Inslow also contains xylitol, a sugar alcohol; sugar alcohols have less impact on blood glucose than regular sugar. In this study, we evaluate whether xylitol also affects the accumulation of visceral fat in mice. In the first experiment, male C57BL/6 mice were fed ad libitum with Inslow powder containing xylitol (0.3, 0.6, 0.9 g/100 kcal) for 8 weeks. In the second experiment, male C57BL/6 mice were fed ad libitum with standard purified rodent diets containing palatinose (0.9 g/100 kcal) and/or xylitol (0.45, 0.9 g /100 kcal) for 8 weeks. In both experiments, visceral and subcutaneous fat was analyzed by X-ray computed tomography (CT) scanner three times during the study period. At the end of the experiment, epididymal, mesenteric, and retroperitoneal fat were weighed, and hepatic lipid (cholesterol and triglyceride) content was measured. In the first experiment, the Inslow powder containing xylitol dose-dependently reduced the fat accumulation in mice according to the X-ray CT analysis 4 and 8 weeks after feeding. The weights of epididymal, mesenteric, and retroperitoneal fat and hepatic lipid in the mice fed Inslow powder containing xylitol were lower than those in mice fed Inslow powder without xylitol. In the second experiment, palatinose and xylitol synergistically reduced the accumulation of fat, demonstrated by the weights of epididymal, mesenteric, and retroperitoneal fat and hepatic lipid. These results suggest that the combination of palatinose and xylitol is an essential factor in Inslow to reduce the accumulation of fat.

P-6

Effects of *Monascus* koji on Rheolgcal Property of Bread

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Pigments produced by *Monascus* sp. have been used as a natural food colorant for fish, bean curd, and wine. *Monascus* koji is produced by the growth of *Monascus pilosus* on rice. In addition to the effects of *Monascus* koji on blood pressure and cholesterol levels have been reported. In this study, effects of *monascus* koji on the microstructure and color tone of bread were investigated by SEM microscopy and measurement of mechanical properties and color tone. Sensory evaluation was investigated the favor of six items. With increasing *monascus* koji concentration, it became more difficult to clearly observe the starch particles of dough,and the gas cell walls of the breads contained many small holes. For breads containing *monascus* koji , hardness was decreased and cohesiveness was increased as compared with bread alone. The color tone of breads shielded from light did not change, but that of breads containing 1.0 to 5.0% *monascus* koji which were subjected to ultraviolet light changed dramatically. Breads containing 0.5% *monascus* koji was ranked higher in terms of color tone, taste, flavor and texture and overall evaluation compared with breads containing 1.0 to 5.0% *monascus* koji and those with no *monascus* koji .

POSTER SESSION

P-7

Effects of Dietary Fiber-enriched Liquid Formula on Postprandial Glycemic Parameters

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Objectives

Dietary therapy for diabetes has changed from "low carbohydrate/high fat" to "reasonable fat restriction" as recommended by the guidelines of the American Diabetes Association. In addition, there is evidence that dietary fiber is useful for diabetics in terms of improving glycemic control. We assessed the effect of a dietary fiber-enriched liquid formula (DIMS) on postprandial glycemic parameters.

Methods

A randomized, single-blind, cross-over, clinical trial was carried out in 19 healthy men aged 30 to 60 years old. Subjects took 200 ml of each of the following at least one week apart; (i) DIMS (carbohydrate 28.6 g, fiber 4.8 g, 200 kcal), (ii) a widely-used liquid formula (MA-8, carbohydrate 28.6 g, fiber 0.8 g, 200 kcal), (iii) glucose solution I (carbohydrate 28.6 g, 114.4 kcal), and (iv) glucose solution II (carbohydrate 50 g, 200 kcal). Blood was collected before administration and at 30/60/90 and 120 min after administration. Then the plasma glucose and serum insulin levels were measured.

Results

The area under the curve for glucose after administration of DIMS was significantly decreased in comparison with that of MA-8 or glucose solution I (1,395±1,189 mg/dl · min vs. 1,807±1,116 and 2,006±1,191 mg/dl · min, respectively) although the amount of carbohydrate in the three diets was equal. In contrast, the area under the curve for insulin after administration of DIMS was slightly larger than after MA-8 and was significantly larger than with glucose solution I.

Conclusions

Postprandial glucose uptake was significantly lower with DIMS than MA-8. DIMS may be useful in dietary therapy for diabetes to improve glycemic control.

POSTER SESSION

P-8

Aloe Vera Gel Extracts Activate PPARs Transcription Activities

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Purpose

Aloe vera is a widely used herb that has various effects. Aloe vera gel is widely consumed as a functional food material. We confirmed that oral ingestion of aloe vera gel shows an anti-diabetic effect as well as body fat reduction effect in type II diabetic model animals, and we also identified five effective molecules. The peroxisome proliferator-activated receptors (PPARs) are ligand-activated transcription factors implicated in the metabolism of both carbohydrates and lipids. Therefore, we investigated PPARs in this study, and the PPAR activity of aloe vera gel extracts was examined using luciferase reporter assay.

Methods

1. The luciferase assays were performed using a GAL4/PPARs chimera system. In brief, we transfected p4xUASg-tk-luc (a reporter plasmid), pM-hPPARα, -hPPARγ, -hPPARδ (an expression plasmid for a chimera protein for GAL4 DNA-binding domain and each human PPAR-ligand-binding domain), and pRL-CMV (an internal control that normalizes transfection efficiencies) into CV-1 cells cultured on 96-well tissue culture plates. Twenty-four hours after transfection, the transfected cells were cultured in media containing each extract or compound for an additional 24 hours. Luciferase assays were performed using the dual luciferase assay system.
2. C57BL/6J mice were divided into two groups, and fed a standard diet or a high-fat diet. The mice were orally administered vehicle as a control solution or 40_g/mouse/day of aloe vera gel extract. After 24 weeks, DNA microarray analyses were performed using mRNA extracted from fat, liver and muscle of these mice.

Result and Discussion

1. Samples from the mice fed aloe vera gel extract showed activation of PPARα, γ and δ in a dose-dependent manner.
2. On DNA microarray analysis, there were 1,961 fat genes, 2,709 liver genes, and 1,151 muscle genes showing a two-fold or higher change in the group with aloe vera gel extract intake compared with the respective levels in the high fat diet group. Many of these genes are assumed to be related to energy metabolism. We will perform a detailed gene expression analysis using real-time RT-PCR, and clarify the anti-diabetic effect and the body fat reduction effect of aloe vera gel, including its relation to PPAR activation.

POSTERSESSION

P-9

Effects of Tea Catechins on Body Fat and Serum Malondialdehyde-low Density Lipoprotein

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Background and Objectives

Catechins, the major component of green tea extract, have various physiologic effects. Recently, there are a few studies on the effects of catechins on body fat reduction in humans. On the other hand, it has been reported that the body mass index (BMI) correlates with malondialdehyde and thiobarbituric acid-reactive substances in the blood. The aim of this study was to evaluate the effect of tea catechins on body fat and serum malondialdehyde-low density lipoprotein (MDA-LDL) in Japanese male subjects by a clinical trial.

Method

Japanese male subjects (BMI: 24.9±0.3kg/m^2) ingested a beverage containing 690mg (690mg group, n=17) or 20mg (20mg group, n=18) tea catechins daily for 12weeks. Anthropometric parameters, abdominal fat levels (estimated by CT scan) and biochemical blood parameters were measured.

Results and Discussion

BMI, waist and abdominal fat levels were significantly lower in the 690mg group compared to the 20mg group. Changes in body fat parameters and changes in MDA-LDL were correlated at 12weeks. These results suggest that the accumulation of body fat might be associated with an increase of lipid oxidizability, and that a redox regulatory system might be involved individually in the body-fat and MDA-LDL reducing effects of catechins.

Conclusion

Daily intake of tea catechins reduced abdominal fat. This reduction might be related to the anti-oxidant effect of tea catechins. Tea catechins might be useful in the prevention and treatment of obesity.

POSTERSESSION

P-10

Effects of Tea Catechins on Risk Factors of Metabolic Syndrome

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Background and Objectives

Obesity is considered to reside upstream of metabolic syndrome leading to various lifestyle-related diseases. So far, we have investigated the body fat-reducing effect of tea catechins by several double-blind controlled trials. The aim of this study was to evaluate the effect of tea catechins on risk factors of metabolic syndrome in Japanese obese subjects by a pooled-analysis of these clinical data.

Method

Three double-blind controlled clinical trials were conducted by two contract research organizations, Japan. Using data from these trials (Control group: n=187; female/male=82/105, Catechin group: n=196; female/male=88/108), we performed an individual patient data pooled-analysis, since each study protocol was almost the same. Common protocol was as follows: Subjects ingested for 12 weeks test beverage containing either a high (Catechin group: 577.6mg) or a low (Control group: 85.1mg) catechin concentrations (340ml/d). The subjects maintained their dietary intake and exercise at a constant level during the study period. Supplemental pills and/or foods that influence glucose or lipid metabolism were prohibited.

Results and Discussion

Subjects were obese, mean body mass index (BMI) $\geq$ 25 kg/m^2, as defined by Japan Society for the Study of Obesity. The baseline characteristics and daily energy intake (both at week 0 and 12) were not different between the treatment groups. Changes (mean $\pm$ SEM) from baseline values of BMI, waist circumference, total fat area, and visceral fat area after 12 weeks of treatment were -0.09 $\pm$ 0.05 kg/m^2, -0.50 $\pm$ 0.22 cm, -1.60 $\pm$ 2.70 cm^2, and -3.20 $\pm$ 1.80 cm^2 in the Control group, -0.58 $\pm$ 0.04 kg/m^2, -2.22 $\pm$ 0.16 cm, -19.06 $\pm$ 2.89 cm^2, and -11.28 $\pm$ 1.55 cm^2 in the Catechin group, respectively. There were significant differences between the treatment groups in changes of these items during 12 weeks. In subjects in the Catechin group, but not the Control group, with baseline values of serum fasting glucose over 110mg/dl, total cholesterol over 220mg/dl, LDL-cholesterol over 140mg/dl, or systolic and/or diastolic blood pressure over 130mmHg/85mmHg at week 0, there were significant decreases in these parameters at week 12.

Conclusion

Daily ingestion of tea catechins apparently reduced body fat and might decrease the risk of metabolic syndrome leading to various lifestyle-related diseases.

POSTERSESSION

P-11

Effects of Diacylglycerol Oil on Adiposity in Obese Children

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Background and Objectives

Since it is reported that pediatric obesity is very likely to progress to adult obesity, it is important to take preventive measures in the early childhood. Several studies have shown that diacylglycerol (DAG) oil may suppress accumulation of body fat in adults compared to triacylglycerol (TAG) oil. In this study, we investigated the effect of DAG oil as part of dietetic therapy on obese children.

Method

The subjects were 11 male and female obese children who were under treatment at the outpatient clinic (boy: 4, girl: 7, age: 7-11 years old). Daily-use cooking oil was changed to DAG oil, and the effects on the abdominal fat area and serum lipids were investigated.

Results and Discussion

There were no significant differences in the daily calorie intake or lipid intake between before and after ingestion of DAG oil. The Rohrer index did not change after use of DAG oil for five months, but the total and subcutaneous fat areas significantly decreased in the 5th month after ingestion of DAG oil. Additionally, although no significant difference were observed in the visceral fat area, the visceral fat area tended to decrease ($p=0.062$). Leptin was significantly lower than the initial level after ingestion of DAG oil.

Conclusion

The ingestion of DAG oil decreases both the abdominal fat area and leptin in obese children, suggesting that DAG oil prevents obesity in children as well as adults.

POSTERSESSION

P-12

Effect of Diacylglycerol Oil Containing Plant Sterols on Serum Cholesterols in Patients on Pravastatin (10 mg/day)

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Background and Objectives

Statins inhibit the hepatic cholesterol synthesis; however, statins tend to increase the intestinal cholesterol absorption due to the feedback effect. Therefore, we examined the additional dietary treatment involving plant sterols (PS, a cholesterol absorption inhibitor) on blood cholesterol concentrations in hypercholesterolemic patients on pravastatin therapy (10 mg/day).

Method

The patients (n=61) were randomly assigned to one of three groups, who consumed triacylglycerol (control), diacylglycerol (DAG) or DAG containing PS oils as a cooking oil (~10 g/day) for 12 weeks.

Results and Discussion

The average intake of PS from the PS/DAG oil during the test period was significantly higher than that for TAG and DAG oils (502 vs. 49 and 38 mg/day, $P<0.05$). Significant cholesterol-lowering effects from the baseline were observed in the case of the PS/DAG oil treatment alone. No effects on serum triacylglycerol and high-density lipoprotein cholesterol concentrations were observed in the three treatments. In the PS/DAG oil treatment, a clear inverse correlation between changes in serum LDL cholesterol concentrations and baseline serum campesterols (a marker of cholesterol absorption) was found.

Conclusion

A combination of PS/DAG oil and pravastatin may be a useful strategy for further ameliorating blood cholesterol concentrations for hypercholesterolemic patients with a low response to pravastatin.

POSTER SESSION

P-13

Effect of the Dried-bonito Broth (Katsuo-bushi Dashi) on the Quality of Life (QOL) in Elderly Subjects: the Effect on the Physical Condition, Emotional States, Blood Pressure and an Oxidative Stress Marker

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POSTERSESSION

Introduction

Dried-bonito broth (DBB; katsuo-bushi dashi) is a basic seasoning in Japanese cuisine and is used as a traditional remedy for recovery from fatigue. Previous human trials have indicated that ingestion of DBB improves mood states such as fatigue and tension-anxiety.

Objective

To investigate the effect of DBB on QOL (quality of life) including physical condition, emotional states, blood pressure, and oxidative stress which is reported to be related to fatigue in elderly Japanese subjects by a randomized crossover trial.

Methods

The subjects were elderly inpatients (n=27, 83.3 ± 8.8 years old, 8 men and 19 women) at a hospital or nursing service facility. The subjects ingested commercial DBB (Hondzukuri-ichibandashi, Ajinomoto Co., Inc.) or water (125 mL per day) for one month. The physical condition and emotional states were evaluated by medical doctors or nurses with a 4-point scale before and after the ingestion periods. The measurement of blood pressure and urinary 8-hydroxydeoxyguanosine (8-OHdG), an oxidative stress marker was also performed before and after the ingestion periods.

Results and Discussion

Evaluation of physical condition and emotional states indicated that diarrhea ($p<0.05$) and composure ($p<0.05$) significantly improved during the ingestion of DBB. The score of fatigue after ingestion of DBB tended to be lower than that after water ingestion ($p<0.1$). Systolic blood pressure decreased significantly during DBB ingestion ($p<0.05$). Urinary 8-OHdG significantly decreased during DBB ingestion ($p<0.001$). No significant changes in physical condition, emotional states, blood pressure and 8-OHdG contents were observed during the water ingestion. These results indicate that DBB could improve physical condition and emotional states, lower SBP and reduce an oxidative stress.

Conclusion

These results suggest that ingestion of DBB could improve the QOL of elderly subjects

P-14

Effect of Maternal Severe Dietary Restriction on the Growth and the Blood Glucose Response in Offspring Rats

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Introduction

In Japan, slim young women increased recently. Furthermore, low weight birth babies are increasing. Barker and colleagues showed a relationship between birth weight and adult disease, including facets of the metabolic syndrome. Ravelli AC et al reported that the exposure to the Dutch famine during late gestation was associated with increased adult obesity and glucose intolerance. Beside the famine exposure early in gestation resulted a high incidence of hypertension. But the mechanism of relationship between fetal nutrition and adult disease are unclear. In this report, we investigated the effect of maternal severe dietary restriction on the growth and the blood glucose response in offspring rats.

Experimental design

Female and male wistar rats (9week-old) were used. Female rats were mated with male rats, and the determination of pregnancy was conducted by smear test for sperm. Following the impregnation, female rats were divided three experimental groups. The first group was control group which was permitted free access to food throughout gestation and lactation period. The second group was dietary restricted group which permitted to intake 50% of consumption by control group during the middle gestation. The third group was dietary restricted group which permitted to intake 50% of consumption by control group gestation during the late gestation. After pup's birth, the litter size were arranged to 10. And naso-tail top length was measured. Both body weights of dams and pups were measured from 4th day to 20th day. Pups were weaned at 21th day. After birth, blood glucose response were measured by glutest cencer on 60th day.

Result

Naso-tail length at a 4 day-old pups was larger in second group in comparison to control rats. Glucose concentrations were rapidly increased 15 min after oral administration glucose in second group and third group in female pups. Female pups of second and third group showed augmentation of body weight at 60 day of age compared with control group.

POSTERSESSION

P-15

Monitoring of Sodium and Potassium Content in Restaurant Foods

J. B. Hwang, H. S. Kim, W. J. Cho, D. H. Kim, D. G. Leem, S. H. Kim and D. B. Kim

Busan Regional KFDA

In this study, the content of sodium and potassium in restaurant foods (steakes, ribs, pastas, salads, sea foods and soups) were determined by atomic absorption spectrometry after microwave digestion. The samples were purchased from five major familiy restaurants (OUTBACK, TIGF, VIPS, Bennigans and Sizzler) in Korea. The calibration concentration range was set at 0.1~2.0 μg/mL(R^2>0.998) for sodium and 0.1~3.0 μg/mL (R^2>0.999) for potassium. The limit of detection (LOD) for sodium and potassium was formed to be 8 μg/L and 6 μg/L, respectively and the limit of quantitation (LOQ) was 26 μg/L for sodium and 18 μg/L for potassium. The sodium and potassium contents in six food items such as steakes, ribs, pastas, salads, sea foods and soups were analysed. Pastas showed the highest sodium (1696.7mg/dish) and potassium (924.5mg/dish) content among all 6 items and soup has the lowest sodium (534.7mg/dish) and potassium (195.5mg/dish) content. We also analysed sodium and potassium content in side dishes such as baked sweet potato, baked potato, french fries, steamed vegetables, fried shrimp and stir-fried rice. The resulting average contents of sodium and potassium were as follows: 138.3mg/dish and 816.1mg/dish in baked sweet potatoes; 84.8mg/dish and 746.2mg/dish in baked potatoes; 590.1mg/dish and 586.4mg/dish in french fries; 170.6mg/dish and 377.5mg/dish in steamed vegetables; 466.0mg/dish and 62.5mg/dish in fried shrimps; and 779.1mg/dish and 211.7mg/dish in stir-fried rice, respectively.

POSTERSESSION

P-16

Study of Suitable Physical Properties of Food for Dysphagic Patient

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Background

Patients with dysphagia indicated reduction in the serum albumin. As this cause, it may be difficult to suitable physical properties of food for dysphagic patient. Therefore it is important suitable physical properties of food for dysphagic patient.

Seirei Mikatahara General Hospital is one of the most experienced hospitals about nutritional management for dysphagic patients in Japan. In the hospital, there are 5 grades (level0-level4) of stepwise swallowing foods for dysphagic patients. Classified 5 graded of stepwise swallowing foods decide their clinical experience. From level 0 to level 2 indicated uniform matter are provided for severe dysphagic patients. Level 3 and level 4 are heterogeneous mixture.

Objectives

We research physical properties of classify 5 graded food. It is possible for serve suitable food for each dysphagic patient.

Methods

There were 165 foods in classify 5 graded of stepwise swallowing. We measured physical properties of these foods using CREEP METER (YAMADEN RE2-3305B), and calculated hardness, adhesiveness, and cohesiveness.

Results

	L0	L1	L2	L3	L4
Hardness (N/m^2)	2,000～7,000	1,000～10,000	Less than 12,000	Less than 15,000	Less than 40,000
Adhesiveness (J/m^3)	Less than 200	Less than 200*	Less than 300**	Less than 1,000	Less than 1,000
Cohesiveness	0.2～0.5	0.2～0.7	0.2～0.7	0.2～0.9	0～1.0

* In case of cohesiveness around 0.4 can adapt less than 500 of adhesiveness

** In case of cohesiveness around 0.4 can adapt less than 800 of adhesiveness

POSTERSESSION

P-17

Study of Gelling Agents to Make Test Food for Videofluorography

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Background

Seirei Mikatahara General Hospital is one of the most experienced hospitals about nutritional management for dysphagic patients in Japan. In the hospital, there are 5 grades (level0-level4) of stepwise swallowing foods for dysphagic patients. Foods (level0-level2) indicated character of uniform matter, like jelly, are provided for severe dysphagic patients. It needs skills to judge which patient suitable for which grade of swallowing foods in clinical staff. As the assessment of dysphagic function, videofluorography is widely performed. And this assessment use test food with barium sulfate. However, barium sulfate may change texture of food. Therefore we think there is no suitable test food for stepwise swallowing.

Objectives

Our aims were ① to investigate how much barium effect food texture and ② to determine concentrations of gelling agents for test foods which were suitable for level0-level2 of 5 grade of stepwise swallowing foods.

Methods

We used liquid barium diluted into 50w/v% with ion exchanged water and made test food using various concentration of gelling agent. To make test food, we heated gelling agent for a minute boiled, and it kept incubating 6h at 20°C. Measurement of textures was used CREEP METER (YAMADEN RE2-3305B), and calculated hardness, adhesiveness, and cohesiveness.

Results

Influence of barium: Hardness of 1.5% and 3.0% of gelling agents barium jelly were significantly lower compared without barium ($p<0.05$, t-test). Cohesiveness of 3.0% of gelling agent barium jelly was significantly higher compared without barium ($p<0.05$). Cohesiveness of 1.5% of gelling agent barium jelly and adhesiveness were no significance.

Concentration of gelling agent for test foods: Correlation between hardness and concentration was significantly ($r=0.99$, $p<0.05$). Calculated concentrations by regression curve were tested whether they were appropriate for textures of test foods. Finally, we decided that test food for lower limit and upper limit for each level. Level0 was 0.95% and 1.60% of gelling agents, respectively. Level1 was 0.65% and 1.95%. Level2 was 0.45% and 2.20%.

Conclusions

We found that texture of jelly was influenced by barium. This result indicated the necessity of standardized test foods for dysphagic patients. Accordingly, we determined concentrations of gelling agents for test foods which were suitable for stepwise swallowing foods. We thought it would bring about clinical benefits for assessment of dysphagic function.

POSTERSESSION

P-18

The Effect of the Daily Physical Activity and Nutritional Intake on the QOL in an Elderly Community-dwelling

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[3] Jumonji University,
[4] Tokyo University of Agriculture

Objective

The goal of this study is to clarify the significance and effect of the physical activity and nutritional intake on the QOL.

Design

Cross sectional study

Setting

N town, Gunma Prefecture, Japan.

Participants

303 community-dwelling elderly persons.

Method

Anthropometric measurements, daily physical activity including walk counts, usual walking time, and maximum walking time, the daily nutritional intake as determined by a food frequency questionnaire, and the QOL scores based on an SF-36 questionnaire were all evaluated.

Results

The QOL score was significantly lower in old-old females than in young-old females. The usual walking time and maximum walking time were significantly higher in old-old females than those in young-old females. The daily intake of energy and salt was significantly lower in old-old males than in young-old males.

As a result of a partial correlation analysis to control for individual sex and age, the slower the usual walking speed, and the slower the maximum walking speed, the lower QOL scores.

However, there was no correlation between the QOL score and the nutritional intake.

Conclusion

The quality of daily physical activity was therefore determined to be one of the most important factors for maintaining the QOL scores in the elderly.

POSTER SESSION

P-19

Effect of High-fat Diet Induced Obesity on Inflammatory Factors in Aged Mice

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Objective

Obesity accelerates the inflammatory reactions, which may affect to pathological process of various diseases. Recent National Nutrition Survey in Japan reported that the incidence of obesity was increased especially in middle-aged men. However, it is not fully understood about the effect of obesity on aging. Then, we investigated the effect of high-fat diet induced obesity on inflammatory factors in aging.

Methods and experimental protocol

We set up following 3 old groups of C57BL/6 mice, fed by each experimental diet from 5 weeks of age. (1) Old group: mice received standard diet for 19 months. (2) Old-diet group: mice received high-fat diet for 6 months (until middle age) and subsequently received standard diet for 13 months. (3) Old-high-fat group: mice received high-fat diet for 19 months. Mice received standard diet until 7 weeks of age were used as Young group. In total 4 groups of mice, adipose tissues and other organs were weighed and inflammatory factors in sera were measured.

Results

Although old-high-fat group revealed severe obesity until 16 months of age, some of mice in the group lost the weights rapidly afterwards. Analyzing 3 groups (old group, old-diet group, and young group) of mice, body weight of old-diet group subsequently decreased comparable level to old group by feeding standard diet, though obesity was induced in old-diet group during high-fat diet until middle age. Final body weight was not different between old group and old-diet group, however, old-diet group showed significantly increased peritoneal adipose tissue weights compared with old group. Serum insulin, CRP, and MCP-1, were increased in both old and old-diet groups compared with young group, while old-diet group showed higher serum MIP-2 and leptin levels compared with old and young groups of mice.

Conclusion

High-fat diet induced obesity in middle age may affect inflammatory profiles in subsequent aged stage.

POSTERSESSION

P-20

A Longitudinal Study of the Effect of Lifestyle on Bone Mass in Adolescence

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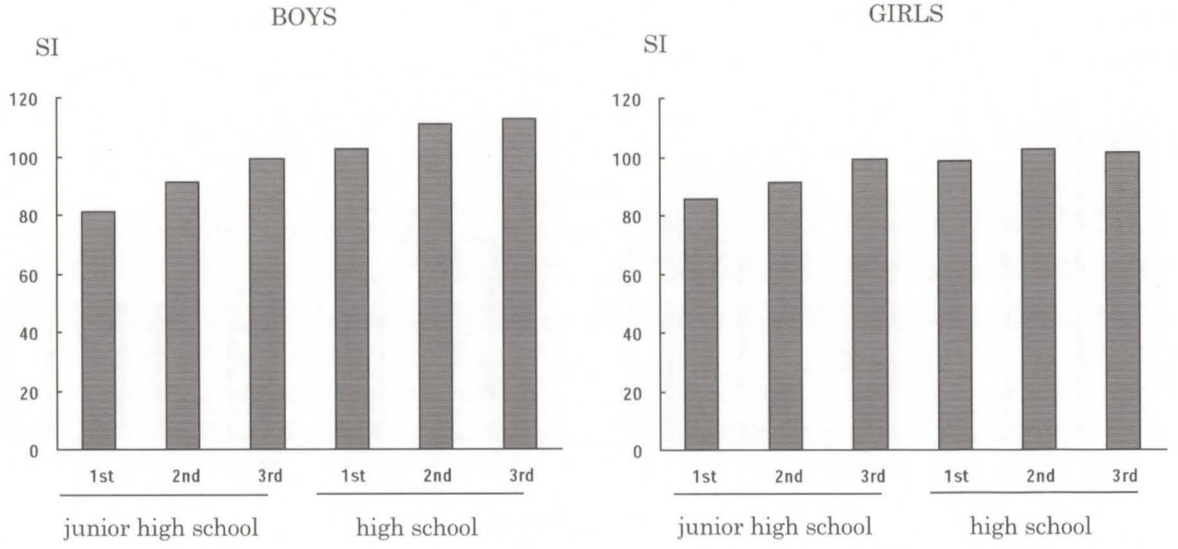
It is essential to obtain the higher amount of the peak bone mass (PBM) early in life in order to prevent bone loss later in life. The periods during junior high and high school are considered to be very important because the PBM usually reaches at these periods. Therefore, it is hypothesized that lifestyles in these periods affects the amount of PBM. In order to examine this hypothesis, we analyzed the relation between the bone mass (BM) changing and lifestyles from 1st grade in junior high school to 3rd grade in high school.

Subjects were the students (272 boys and 263 girls), who went to a consistent junior and high school in Tokyo Metropolitan area and also completed the all years data. The BM of the right calcaneus was measured at annual medical examinations on April using Imaging Bone Ultrasonometer (GE Yokokawa Medical System, Achilles Insight™). We took the stiffness index (SI) as a BM. At the same time, we measured their heights and weights and performed a self-recording questionnaire about their lifestyles (exercise and physical status, etc.) and a food frequency questionnaire.

The figure shows the stiffness index during 6 years. Much frequent exercise, higher milk intake and much rarely skipping breakfast were associated with greater BM increase. It was thus confirmed that exercise and adequate food intake during growth periods are important to increase PBM.



P-21

A Study of the Effects of Milk Consumption and Exercise on Bone Mass in High School Students

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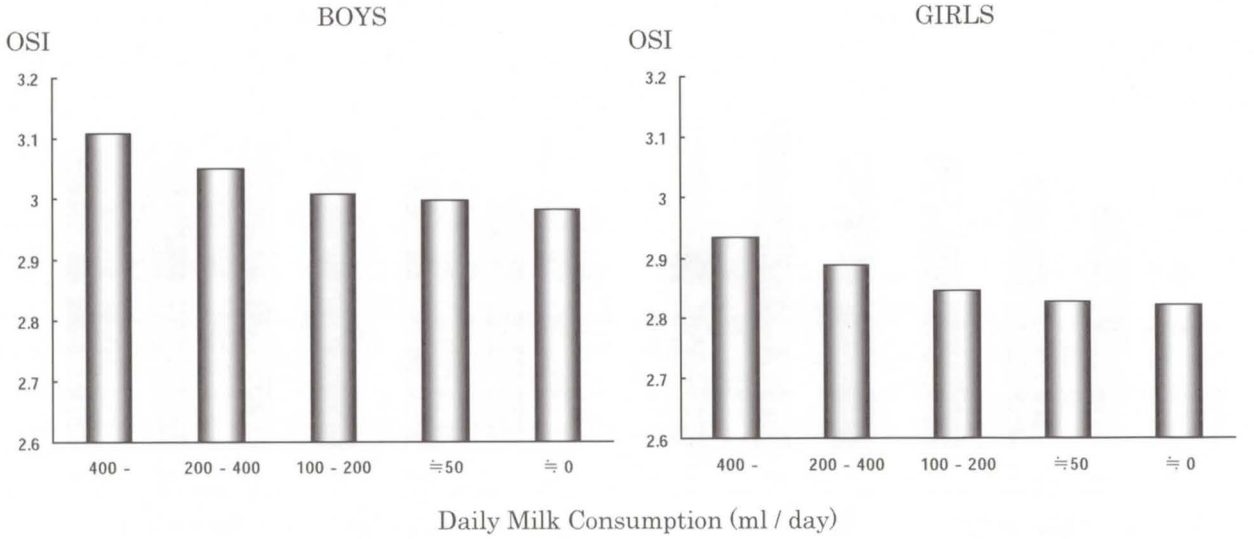
It is essential to obtain the higher amount of the peak bone mass (PBM) early in life in order to prevent bone loss later in life. The periods during high school are especially important because PBM usually reaches at these periods. It is hypothesized that previous as well as present lifestyle affects the amount of PBM. In order to examine this hypothesis, we studied the bone masses (BMs) of high school students and their relations to the lifestyles using the data of the bone mass measure project carried out in Japan from 2005 to 2006.

Subjects were high school students (12,061 boys and 22,265 girls), who completed the data of BMs and also questionnaire of lifestyles. The BM of the right calcaneus was measured using ultrasound bone assessment systems (ALOKA, AOS-100). We used the calculated osteo sono-assessment index (OSI) as the BM. At the same time, we performed questionnaires on present and previous milk consumption, exercise practice, histories of bone fracture and customs of breakfast taking.

As a result, the BM increased in 3 years during high school. Milk consumption in the periods during elementary and junior high school and those of today affected the BMs. Higher milk intakes were associated with greater BMs. The previous and present exercise frequencies were also bound to influence the BMs. The group with skipping breakfast had lower BMs than that without skipping. These results suggest that lifestyles of not only current time but also elementary and junior high ages influence BMs in present high school ages. Therefore, lifestyle guidance from younger children ages is required.

POSTERSESSION



P-22

Superheated Steam Healthy Cooking

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Purpose

With life style of health and sustainability (LOHAS) intention, superheated steam cooking ovens have attracted attention recently. Superheated steam has three heat characteristics, condensation heat capacity, convection heat transfer, and radiation heat transfer, respectively. By using superheated steam, we compared the increase rate of oil from food materials, salt decreasing efficiency, and prevention rate of nutrients in foods which are considered to contribute to human health with those of a conventional oven.

Experimental Methods

We used a water oven, named "Healsio" to prepare some foods. After cooking, fat content, POV in fatty acids, salt concentration, and some vitamin contents were measured. During cooking, the oxygen content was also measured using an oxygen monitor.

Results and Discission

Just 4 minutes after introduction of superheated steam into the oven, the oxygen concentration decreased to 5% and the oxygen level was kept less than 5% during the operation inside the oven. It was possible to prepare high quality meat, fish, breads and other foods. Especially, oil or fat content decreased in all the meat. With the chicken, we found a value of approximately 25% extraction when we compared it with grill cooking. However, it was shown by scan electron microscope the meat tissue was not damaged by superheated steam. In addition, about 20% salt content reduction was obtained in sliced salted salmon. Destruction of vitamin C was restrained and it was confirmed that the oxidation of oils and fats was restrained remarkably. From the above results, we concluded that the superheated steam cooking technology not only could maintain the nutrients in food but also is useful for caloric restriction patients. Furthermore, it was concluded that superheated steam cooking contributes to health maintenance, especially for those suffering from metabolic syndromes.

P-23

Nutritional Physiology of Pantothenic Acid Deficiency with Regard to Intestinal Motility in Aging Rats

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Coenzyme A (CoA) is an essential cofactor in numerous metabolic and energy-yielding reactions and is involved in the regulation of key metabolic enzymes. CoA is also the source of 4'-phosphopantetheine; this molecule is required in several biosynthetic pathways such as fatty acid and carbohydrate syntheses. The CoA-precursors pantothenate and pantetheine (PaSH) were demonstrated to have a prebiotic effect.

Atonic constipation, which is induced by intestinal decompression and stagnation of intestinal motility, is a serious problem in the elderly. In clinical medicine, a disulfide type of pantetheine (PaSH), namely, pantethine (PaSS), is widely used in this condition to increase intestinal motility. The present clinical test indicates that pantothenic acid (PaA) is involved in intestinal motility because PaA and PaSH are the precursors of CoA. Due to the decrease in the rate of synthesis of CoA from PaA, the rate of the biosynthetic reaction in which PaSH is obtained from PaA influences aging. In this study, PaSS aids the recovery of intestinal motility and increases the biosynthesis of CoA; however, these effects are not obtained with PaA. The CoA concentration correlates with the degree of intestinal motility.

In conclusion, PaSS is more effective than PaA in aiding the recovery of PaA-deficient aging rats. These results showed that the rate of biosynthesis of PaSH from PaA was delayed.

POSTERSESSION

P-24

Influence of Lactic Acid Bacteria on Longevity and the Host Defense of *Caenorhabditis elegans*

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This study aimed to develop a convenient model to investigate senescence of host defenses and the influence of food and nutrition. A small soil nematode, *Caenorhabditis elegans*, was grown for 3 days from hatching on a lawn of *Escherichia coli* OP50 (OP50) as the normal food source, and subsequently the nematodes were fed lactic acid bacteria (LAB). The life span of worms fed LAB was significantly longer than that of those fed OP50. To investigate the effect of age on host defenses, 3- to 7-day-old worms fed OP50 were transferred onto a lawn of *Salmonella enterica* serovar Enteritidis (SE) for infection. The nematodes died over the course of several days, and accumulation of SE in the intestinal lumen suggested that the worms were infected. The 7-day-old worms showed a higher death rate during the 5 days after infection compared with nematodes infected at the age of 3 days; no clear difference was observed when the worms were exposed to OP50. We then investigated whether the LAB could exert probiotic effects on the worms' host defenses and improve life span. Seven-day-old nematodes fed LAB from the age of 3 days were more resistant to SE compared to worms fed OP50 until they were infected with SE. This study clearly showed that LAB can enhance the host defense of *C. elegans* and prolong life span. The nematode appears to be an appropriate model for screening useful probiotic strains or dietetic antiaging substances.

P-25

Sesamin Elicits a Distinct Hypocholesterolemic Activity by Synergy with α-Tocopherol: Molecular Logic Demonstrated by Time-course DNA Microarray Analysis

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Sesamin is a major lignan in sesame seed. We previously found that ingestion of sesamin (S) together with α-tocopherol (VE) synergistically reduced the concentration of blood cholesterol in rats given a high-cholesterol diet. To elucidate the molecular mechanism of the effect, we analyzed the gene-expression profiles in liver using a DNA microarray. For two weeks, male SD rats aged 6 weeks old were fed a 1% cholesterol diet (HC) or HC containing 0.2% S, 0.5% VE, or S+VE. Blood samples were collected and livers were excised on days 1, 3, 7, 10 and 14, respectively. Ingestion of S+VE synergistically inhibited the development of increased blood cholesterol, while the S group only showed delayed increase of blood cholesterol. Reduction of the blood cholesterol level was due to the marked reduction of low density lipoprotein (LDL) cholesterol. The gene-expression profile showed clear and significant differences between the S and S+VE groups. In particular, the gene expressions of ATP-binding cassette, sub-family G (WHITE), member 5 (ABCG5) and ATP-binding cassette, sub-family G (WHITE), member 8 (ABCG8) were significantly increased, while the gene expression of Apolipoprotein A-IV (ApoA-IV) was significantly decreased. ABCG5 and ABCG8 form a functional heterodimer to work as a cholesterol efflux transporter contributing to the excretion of cholesterol from the liver. ApoA-IV controls the secretion of ApoB which composes LDL cholesterol. The changes in these gene-expressions were also confirmed by real-time PCR. This study indicates that the cholesterol-lowering mechanism underlying the effects of co-ingestion of sesamin and VE is attributable to up-regulation of the gene expression for cholesterol efflux transporter and down-regulation of that involved in secretion of apoprotein.

POSTERSESSION

P-26

Arachidonic Acid Preserves Hippocampal Neuron Membrane Fluidity in Senescent Rats

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Previous studies indicate that there is an age-dependent decrease in the concentration of arachidonic acid (ARA) in the hippocampus and that the ARA-decline is restored by chronic supplementation of ARA in rats (1). We indicated that long-term dietary supplementation with ARA in 20 mo old rats (OA) effectively restores performance in a memory task and induction of long-term potentiation in the hippocampus to the level of young control animals (YC) (2,3). The present study examined Fluorescent Recovery After Photobleaching (FRAP) in YC, old control (OC), and OA neurons in hippocampal slice preparations (4). Three measures; mobile fraction (Mf), diffusion constant (D), and time constant (τ), were estimated among YC, OC, and OA. Each of these parameters was significantly different between OC and YC, suggesting that membrane fluidity is lower in OC than in YC. In contrast, D and _ were almost comparable in OA and YC, indicating that hippocampal neuronal membranes supplemented with ARA were more fluid than those in OC, whereas the fraction of available molecules remained smaller than in YC. Long-term administration of ARA to senescent rats might help to preserve membrane fluidity and maintain hippocampal plasticity.

(1) B. McGahon *et al.*, *Neuroscience*, **81**, 9-16 (1997).
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(4) T. Fukaya *et al.*, *Neurobiol. Aging*, **28**, 1179-86 (2007).

POSTER SESSION

P-27

The Beneficial Effect of Arachidonic Acid (ARA) and Docosahexaenoic Acid (DHA) Supplementation on Coronary Circulation in Elderly Individuals

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Arachidonic acid (ARA) and docosahexaenoic acid (DHA) are known to be important components of phospholipids and cell membranes. Many epidemiologic studies suggest that dietary polyunsaturated fatty acids (PUFA) consumption decreases the risk for cardiovascular events. The purpose of the present study was to determine the effects of ARA and DHA supplementation on coronary circulation in elderly individuals using measurement of coronary flow velocity reserve (CFVR) before and after taking ARA and DHA.

This was a double-blind, placebo-matched study of 28 Japanese elderly individuals (19 men, mean 65 years) conducted to compare the effects of PUFA (ARA: 240mg/day, DHA: 240mg/day) and placebo (olive oil) on CFVR. Coronary flow velocity (CFV) of the left anterior descending coronary artery (LAD) was measured at rest and hyperemia during adenosine triphosphate (ATP) infusion (0.14mg/kg/min) by TTDE to determine CFVR at baseline and 3 months after taking test supplements and placebo. After 3-month supplementation, CFV during hyperemia was significantly higher in the PUFA than in the placebo group (73 ± 19 vs 64 ± 12 cm/s, $p<0.01$) although no significant difference was found between the two groups in CFV at rest (17 ± 7 vs 16 ± 4 cm/s). Thus, CFVR significantly increased after PUFA consumption (3.85 ± 1.04 vs. 4.46 ± 0.95, $p=0.0023$). A significant positive linear correlation was found between changes in the erythrocyte membrane ARA levels and change in CFVR, but was not found between changes in DHA levels and change in CFVR.

Furthermore, we examined the effects of dietary supplementation of ARA on age-related changes in endothelium-dependent vascular responses in rats to understand the underlying mechanism for the human trial described above. Young male Fisher-344 rats (2-month-old) and aged rats of the same strain (22-month-old) were randomly separated into a control diet group (young control, YC; old control, OC) and an ARA-containing diet group (young ARA, YA; old ARA, OA), respectively. After 2-month feeding period, vascular responses were evaluated using endothelium-intact aortic rings. Acetylcholine (Ach)-induced endothelium-dependent vasorelaxation was attenuated in OC and OA compared with those in YC and YA. ARA supplementation exhibited a slight enhancement of the Ach-induced vasorelaxation in aged rats. Ach-induced vasorelaxation correlated very well with aortic ARA concentrations in aged rats ($p<0.0001$).

The results of this study suggest that PUFA, especially ARA, supplementation has a beneficial effect on coronary circulation.

POSTERSESSION

P-28

Polyunsaturated Fatty Acid Intakes and Fatty Acid Compositions of Plasma and Erythrocyte Membranes: Comparison between Young Females and Elderly Males

Aki Kusumoto[1], Hiroshi Kawashima[1], Yoshinobu Kiso[1], Satoko Matsuzaki[2], Terue Kawabata[2]

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Docosahexaenoic acid (DHA, 22:6n-3) and Arachidonic acid (ARA, 20:4*n*-6) are polyunsaturated fatty acid (PUFA) and major constituent of the cell membrane, and plays important roles in the preservation of physiological function. Fish or fish products contain large amount of eicosapentaenoic acid (EPA, 20:5n-3) and DHA, and yolk, lean and fish contain comparative large amount of ARA. We examined how the intake level of individual PUFA in the n-3 FA and n-6 FA group would affect the composition of EPA, DHA and ARA in four individual lipid fractions of plasma and erythrocyte membranes collected from young females and elderly male subjects. The dietary investigation was performed using photographic dietary records for 28 consecutive days, and on the day following completion of the investigation, blood sampling was conducted for the subjects early in the morning after fasting. In plasma triacylglycerol (TAG) fraction, a correlation was observed between intake of EPA and DHA and the composition of EPA and DHA in the elderly male group, not in the young female group. In the elderly male group, significant positive correlations were observed between DHA intake and DHA composition in plasma, but not with DHA composition in erythrocyte membrane. It was suggested that EPA and DHA would be taken into the phospholipids (PL) preferentially and their supply to plasma TAG was insufficient in the young female group. In the elderly male group, the incorporation of DHA into the membrane was limited, corroborating the expectation that DHA would not accumulate above the allowable value. Regarding intakes and compositions of plasma and erythrocyte membranes of ARA, we compared between young females and elderly males.

POSTER SESSION

P-29

Dietary Energy Ratio Affects the Concentration of Salivary sIgA in the Aged

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[1] Department of Human Nutrition Faculty of Nursing and Human Nutrition, Yamaguchi Prefectural University
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[3] Graduate School of Health and Welfare, Yamaguchi Prefectural University

Purpose

This study was conducted to examine the effects of physical, and mental conditions, dietary life, and social factors on the concentration of salivary IgA in the aged people.

Methods

The subjects were 58 persons, aged 65 or over living in Suoh- Ohshima town,Yamaguchi Prefecture. Data for 50 persons were used for the analysis. Subjects were interviewed on both the mos 8-item short-form (SF8) health survey and Food Frequency Questionnaire (FFQ). We measured anthropometric data such as height (HT), weight(WT), arm circumference (AC), triceps skin fold thickness (TSF), and calf circumference (CC). The physical fitness test of each subject was also measured. Saliva flow rate and sIgA concentration were determined, and sIgA secretion rate was calculatesd. There data were analyzed by using *t*-test or Pearson 's correlation coefficient.

Results

Sex difference was shown in saliva volume and IgA concentration. Saliva volume was much more in men than in women. The women's IgA concentration was higher than that of men. There was no relation between IgA concentration and each body measurement value, and also no relation between IgA concentration and physical fitness values. In only women, positive correlations were shown in the relationships between IgA concentration and cereals energy ratio, and between IgA concentration compensated by using protein concentration and carbohydrate energy ratio. Negative correlations were shown in the relationships between IgA concentration and fat energy ratio and between IgA concentration compensated by using protein concentration and an animal protein ratio and the intake of dark green and yellow vegetable.

Conclusion

In this study, we found that salivary IgA concentration had positive correlations with the energy ratios of carbohydrate and cereal, and negative correlations with fat energy ratio. From these results, this study suggests that Japanese traditional food style is better for the elderly people to maintain and promote health.

POSTERSESSION

P-30

The Effect of Hesperidin Administration to Young Women Suffering from Over-sensitiveness to Cold

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[2] Laboratory of Nutritional Science, Icreo Inc.
[3] National Institute of Health and Nutrition
[4] Showa Women's University

Objective

Over-sensitiveness to cold is a popular physical complaint in young Japanese women. Hesperidin is a natural chemical compound found in citrus fruits, and is known for vaso-dilatation effects. We administered a water-soluble analog of hesperidin, α-glucosylated hesperidin to young women to examine its effect on improving over-sensitiveness to cold.

Subjects and Methods

Thirty-seven college age women were recruited to participate in this study. Of these, ten women were not over-sensitive to cold, according to the criteria by Terasawa, and were not included in the analyses. Three women did not complete the study. A total of 24 subjects went under three tests of the study. First, they took a placebo drink without hesperidin and underwent a measurement of blood markers and skin temperature measurements. On the second test, they took a test drink containing 500mgof α-glucosylated hesperidin, and their blood and skin temperature were examined after 30minutes. On the third test, more than two days after the second, they took the test drink 10hours before the blood and skin temperature measurements. Plasma histamine, catecholamines, and serum hesperetin (hesperidin metabolite) were examined in the blood tests. Skin temperature measurements were done by applying the infrared thermograph. Subjects bathed both hands in cool water (15□) for one minute, and then monitored every 5minutes for half an hour.

Results

Plasma histamine was significantly lower ($p<0.01$) in the second test (1.1 ± 0.5ng/ml) compared to the first (2.1 ± 1.0ng/ml). Serum hesperetin was significantly elevated in the second (11.7 ± 22.3ng/ml, $p<0.05$) and the third tests (134.8 ± 84.4ng/ml, $p<0.01$) compared to the first (1.1 ± 2.2ng/ml). Mean skin temperature before bathing in cool water was unchanged during the three tests. Subjects whose skin temperature recovered equal to or more of the pre-bathing values after 30minutes increased from 3/24 in the first test, to 9/24 in the second and third tests. No positive correlations were observed between serum hesperetin values and skin temperatures or plasma histamine and catecholamines.

Conclusion

Oral hesperidin administration accelerated skin temperature recovery in young women with over-sensitiveness to cold. However, the effect did not correlate with serum concentrations of its metabolite, hesperetin.

Terasawa K. Shoyakugakuzasshi (1987)

POSTER SESSION

P-31

Pilot Study of Single Nucleotide Polymorphisms Related Obesity in Japanese Young Women and an Attitude Survey after a Short-term Education Consciousness Genetic Diagnosis

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Objective

Obesity has reached epidemic proportions in some countries. In Japan, its proportion is also increasing but still remaining lower than other countries. There trends in obesity may relate with background of genetic variation. Pilot study was carried out to determine single nucleotide polymorphisms related obesity in Japanese young women with an attitude survey after a short-term education regarding genetic diagnosis

Methods

Genotyping was carried out on genomic DNA extracted from fingernail samples in 50 Japanese young women using DNA isolation kit. The respondent to a survey were freshmen and sophomore students of Tokyo Metropolitan University, who were finishing "the basic nutrition" as a liberal arts. The questionnaires were executed before and after a short-term education about the basic gene and genetic diagnosis.

Results

Single nucleotide polymorphisms (SNPs) of genes, Peroxisome proliferator -activated receptor gamma 2(PPAR γ 2), beta 3 adrenergic receptor (β 3-AR), uncoupling protein 3(UCP3) and adiponectin were examined. The frequency of Ala 12 PPAR γ 2 polymorphism was 4%, Trp64Arg of β 3-AR was 46% (including 6% homozygote) and none in UCP3 gene. The genotypic distribution of 276 SNP in adiponectin gene was 52% G/G, 38% G/T and 10% T/T. Ninety six percent of respondents were answered that a sufficient education needed for promotion of genetic diagnosis, and 87% wished that the genetic diagnosis make for preventing life-style related disease. On the other hand, respondents concerned protection of information (47%) and increase of medical expenses (33%).

Conclusions

The frequency of SNP s in Japanese was different from other races, and this may associate the lower proportion of obesity in Japan. For practical use of genetic diagnosis on preventing lifestyle-related diseases, enlightening education in nutrigenomic science is recommended.

POSTERSESSION

P-32

Studies of Retarding Effects of Some Phyto-materials on Senescence-Accelerated Mouse (SAM)

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The effect of some phyto-materials on the capability of learning and memory in Senescence-accelerated mice (SAM) and corresponding normal senescence mice (SAM-resistant prons Y-P8) were investigated by conducting tests in the Morris Water Maze (MWM). And the retarding effect of some phyto-materials were determined.

The immunity for blood and spleen by flow cytometry were also examined. The surface phenotypes of the cells were identified using monoclonal antibody in conjunction with a two-color by flow cytometric analysis.

It was observed that control mice (R1) had a tendency of decreasing time required to find the hidden platform (escape latency) as a reference memory paradigm using the MWM. In contrast, senescence accelerated mice (P8) had no changed. It means senescence of P8 accelerating proceeded compared with R1. Additional effects of phyto-materials on the diet were examined using MWM test.

A tendency of decreasing time to get escape latency was observed on the Yamabushitake-added group compared to non-added P8 group.

On the other hand, Yamabushitake-added group had significantly higher percentage of natural killer cells in blood and spleen than P8 group.

These findings suggest that Yamabushitake may contain the retarding efficacious components on brain function and immunity which are decrease with aging.

P-33

Immunohistochemical Changes Related to Ageing and Nutrition in the Mouse Hippocampus

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We investigated the age-related changes in neuronal cell death and effects of ageing and nutrition on the hippocampal CA1 sector in mice using immunohistochemistry. We have reported that the administration of endogenous dipeptide, carnosine, showed dose-dependent neuroprotective effects on hippocampal CA1 sector in mice against age-related changes. Carnosine (β-alanyl-L-histidine) is an endogenous dipeptide and is found in brain and other long-lived tissues of humans at concentrations as high as 20mM. It is demonstrated that carnosine has anti-ischemic activity, anti-glication effect and membrane-protecting properties. In this study, we investigated the effect of carnosine and other functional ingredient of food on age-related histopathological and immunohistochemical alteration in glial fibrillary acidic protein (GFAP), Cu/Zn-superoxide dismutase (Cu/Zn-SOD), neuronal nitric oxide synthase (nNOS) and endotherial nitric oxide synthase (eNOS) protein of the hippocampal CA1 sector and striatum in mice. Histopathological observations showed that neuronal change of hippocampal CA1 neurons, which was observed in aged mice, was preserved by carnosine treatment. Immunohistochemical stainings for nNOS were unchanged. However, immunohistochemical stainings for GFAP, eNOS and Cu/Zn-SOD increased in hippocampal cells of aged mice compared with young mice. Additionally, GFAP immunopositive cells in carnosine treatment mice were preserved compared with aged-control mice. From these observations, we suggest that carnosine is effective on age-related neurodegeneration of hippocampal CA1 sector.

POSTERSESSION

P-34

Lipoprotein Metabolism, Insulin Resistance, and Adipocytokine Levels in Japanese Female Adolescents with a Normal Body Mass Index and High Body Fat Mass

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Investigation

In Japan, the prevalence of obesity is increasing year by year whereas that in young females at the age of 20s and 30s has been constantly decreasing. However, the lipid metabolic profiles and body fat mass have not yet been clearly determined in this subset of the population.

Methods and Results

We determined whole body fat mass using whole body dual energy X-ray absorptiometry and the blood lipid and metabolic parameters in 157 Japanese female University students (21.1 ± 1.9 yrs; mean ± SD). As a result, 31 women demonstrated a normal body mass index but an increased body fat mass. They had higher leptin concentration (7.65 ± 3.42 vs 5.96 ± 3.32 ng/ml, $p<0.01$). They also had significantly higher low density lipoprotein cholesterol (104.4 ± 20.0 vs 91.9 ± 21.2 mg/dl, $p<0.05$) and lower high density lipoprotein cholesterol (73.5 ± 14.5 vs 80.4 ± 15.1 mg/dl, $p<0.01$) than females with normal body mass index and normal body fat mass.

Conclusion

Young Japanese women with a normal body mass index but a greater body fat mass, or so-called "hidden obesity", were thus found to have an impaired lipid metabolism profile and higher leptin levels. These abnormalities may be a risk for future cardiovascular events even in this low-risk population.

POSTERSESSION

P-35

Maternal Zinc Deficiency during Lactation Period Modify the Regulation System of NaCl Preference of Their Developed Pups

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It has been well known that maternal dietary NaCl intake influences weaning rats' salt preferences, and brief exposure to NaCl during early postnatal development enhances adult intake of sweet and salty compounds. However, few data have been published concerning about the maternal milk nutrients such as zinc level and later NaCl preference in their developed pups. We have already shown that short term zinc deficiency clearly causes the increase of NaCl preference, so we demonstrated whether or not the maternal zinc deficiency during lactation period cause grown rats' NaCl preference using this zinc deficient system with SD/Slc rats. Zinc deficient (0.7 mg Zn/Kg) , Low zinc (4.0 mg Zn/Kg), and Zinc sufficient as a control (33.7 mg Zn/Kg) diets were fed to the lactating mother during lactation period only (for 3 weeks after birth), and Zinc sufficient diet was fed to the all group's rats after weaning. With water and 0.5M NaCl solution 2-bottle preference experiment was undertaken, and was shown that maternal low-zinc diets during lactation period caused the increased 0.5M NaCl preference in their developing pups up to 11 week-old (after 8 weeks from weaning), even though after their recovery from zinc deficiency. After weaning, significantly increases of norepinephrine (NE) and epinephrine (E) in central nucleus of amygdala (CeA) and decreased plasma oxytocin concentration were observed in Low-Zn group. However, it was confirmed that oxytocin secretion ability after NaCl loading was not impaired in the Low-Zn groups, whereas the NE and E secretion signaling mechanism should be further clarified.

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POSTERSESSION

P-36

The Measurement of Diet-induced Changes in Cognition: Methodological Aspects

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P-37

Evaluation of Fluoride Exposure by Intake Krill

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Krill is a kind of animal plankton living in the ocean and is a shrimp-like crustacean having a length of as much as 6 centimeters. Recently, using of krill is increasing as healthy food material. High concentration of Fluoride (>2000ppm) has been measured in the exoskeleton of krill. In human, a small amount of fluorides can help prevent dental cavities, but high levels of it can result in tooth and bone damage. In teeth and skeletal tissue, fluoride becomes incorporated into the crystal lattice. Excessive fluoride during the period of teeth formation (before 8 years of age) can cause dental fluorosis. In this study, all of the consumed shrimp was assumed as krill and then we calculated fluoride intake level through krill which has 330 ppm of fluoride level in the whole body. It was reported that average daily intake of shrimp was 13g per person (KFDA, 2005). As the result, average 4.3 mg fluoride would be taken a day. This value was below the level which WHO proposed as DRI 5 mg/day for adult. However, it could exceed WHO's value if we take fluoride from other foods, drinking water and dental clinic etc. into consideration. Also, it exceeded children's DRI (1.5 mg/day). WHO reported that fluoride could be decreased in krill if head and exoskeleton were removed. The decrease rate would be 84% (WHO). 0.7 mg of fluorine per day would be taken through the krill without exoskeleton and head. This value is much lower than whole krill's.

In conclusion, it was recommended that krill without exoskeleton and head be taken through the food stuff materials.

POSTERSESSION

サテライト・シンポジウム「食品成分・素材の安全性の考え方」

2007年11月2日
国際連合大学 ウ・タント国際会議場（東京・青山）

主　催：特定非営利活動法人 国際生命科学研究機構（ILSI Japan）
国際アミノ酸科学協会（ICAAS）

【基調講演】

食品の安全と安心のためのリスクアナリシス

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2001年のわが国初の牛海綿状脳症（BSE）発見とその後の大きな混乱を契機にして食品安全基本法が制定され、リスク評価機関として内閣府に食品安全委員会が設置された。この法律で採用されたリスク分析の原則はリスクを健康に被害がないレベルまで削減することであって、必ずしもゼロにすることではない。このようなリスク管理策により日本の食は極めて高い安全性が保たれ、唯一の健康被害が食中毒である。一方、消費者に対するアンケート調査では食品添加物、残留農薬、そしてそれらによる汚染が疑われた外国産野菜などが嫌われた。しかし、これらの化学物質は厳しく規制され、健康被害は発生していない。リスクの大きさと不安が一致しない、あるいは安全と安心が乖離している状況が起こっているのだ。安全な食品に不安を感じる第1の原因は情報の不足である。化学物質の安全性は用量作用関係の原則に沿って行われる。そしてこの原則を理解するためにはかなりの科学の知識が必要である。多くの人は本能的に「良く分からないものは敬遠しておいた方が無難」と考える。第2の原因は「ゼロリスク神話」である。多くの人が天然の食品は安全であり、農薬や添加物が危険をもたらすと誤解している。普通の食品がガンの最大の原因であることや、野菜や果物が残留農薬基準よりずっと多い量の天然の農薬ともいうべき化学物質を持ち、その多くが発ガン性であることを知る人は少ない。生産と消費の距離が大きく離れたことも、ゼロリスク神話を強めた。第3の原因は、情報の混乱である。例えば「無添加・無農薬」で商品を差別化して売り上げを計る企業も多い。もちろん、無添加・無農薬が健康にいいことを証明した科学論文はないのだが、これが「食品添加物や残留農薬は危険」という誤解を広げている。安全とは無関係の表示等の形式違反であっても食品の大量回収と大きな報道になり、それが「危険だから回収された」という誤解を広げる。安全と安心を一致させるために必要なことは、食品の安全を理解するための科学的知識の普及とともに、氾濫する情報のなかから科学と偽科学を見分けるための科学リテラシーの向上である。第2に、食の安全を守るためには、農場から食卓までのすべての関係者が「安全」という目標を共有して協力するリスクコミュニケーションの実施であり、とくに事業者と消費者の真剣な協議が必要である。最後に最も重要なことは、安心は安全と信頼の2つから成り立っていることである。食品関係事業者の小さな法律違反も消費者の信頼を失い、食品に対する不安を大きくすることを銘記すべきである。

[KEYNOTE LECTURE]

Risk Analysis for Safety of Foods and Ease of Mind of Consumers

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The first bovine spongiform encephalopathy (BSE) case in Japan in 2001 and following big confusion forced our government to establish the new food safety law and to install the Food Safety Commission as the independent risk assessment organization. The principle of the risk analysis adopted by the new law is to reduce risk to a level which does not damage human health but not to zero. Using this method, safety of foods in Japan is kept at a very safe level except for food poisoning. However, surveys indicate that consumers feel anxiety to food additives, pesticide residues, and vegetables imported from foreign countries which might be contaminated by these chemicals, in spite of the fact that the use of these chemicals are strictly regulated and there are no reports on health hazard caused by the chemicals in foods. The anxiety seemed to be caused by several reasons. The first reason is insufficient information. The safety of chemicals is based on the principle of dose-response relationship and scientific knowledge is necessary to understand this principle. People instinctually classify something they don't understand as unsafe. The second reason is the "zero risk myth". Many consumers misunderstand that natural foods are safe and food additives and pesticide residues are making food dangerous. Few persons know that ordinary food is the major cause of cancer, and that vegetables and fruits contain "natural pesticides" the amount of which is much larger than pesticide residues and some of them are carcinogenic. Increase in the distance between the places of food production and food consumption further strengthens the zero risk myth. The third reason is the misunderstanding information. Many companies are selling the "additive-free and/or pesticide-free" diets. Although these chemicals are safe if used following regulation, such a sales strategy persuades consumers that these chemicals are dangerous. To decrease anxiety on foods, it is necessary to improve the scientific literacy to discern sound science and bad science and also to increase the scientific knowledge to understand the risk analysis method. In addition, risk communication among stakeholders is necessary to talk about the level of acceptable risk. The most important fact is that ease of mind of consumers is consists of two factors, safety and trust. It should be noted that only small lawbreaking makes food-related companies to loose trust of consumers and increase anxiety about foods.

食品成分・素材の安全性評価の考え方

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特定の物質がヒトに対してどの程度に安全であるかは、その物質についてリスクアセスメントの結果に基づいて判断される。ここでリスクアセスメントとは、それぞれの時点において入手可能な科学的知見を基盤にして、対象とする物質のヒトに対する有害影響を質的および量的に評価するための科学的手続きで、通常、次の4段階の手段で進められる。

1) 有害性確認：対象とする物質がヒトに対してどのような有害影響を起こす性質を潜在しているかを判断する段階
2) 有害性特定：対象とする物質がもっている有害性の強さと作用メカニズムを判断する段階
3) 曝露評価：ヒトは対象とする物質とどのように接触するか（例：接触経路、摂取量、摂取機関など）を判断する段階
4) リスク特定：上記3段階での判断を総合して、①対象とする物質が、日常の接触条件（例：摂取条件）でヒトに対してどの程度のリクスを及ぼすか?　もしくは②対象とする物質は、どの程度の接触条件（例：摂取条件）ならばヒトに対してリスクを及ぼさないとみなされるかを特定する段階

実用的見地からすると、リスクアセスメントは対象とする物質によるヒトの健康被害に対処し、それを予防する方法あるいは論理を準備する目的で実施される。従って、食品成分／素材についてのリスクアセスメントの最終的な目標は対象とする物質の摂取上限量を確定するための科学的知見と科学的論理を提供することにあるといえる。

上限摂取量ULは、本来、栄養成分を対象とした安全性指標で、一般ヒト集団の殆どの全ての個体が有害影響を伴うことなしに生涯にわたって摂取可能な最大一日摂取量を意味する。ULの算定には、新しい食品添加物の許容一日摂取量ADIの場合と同様に、動物試験などでの無毒性量NOAELと不確実係数UFを適用した以下の数式が用いられる。この場合、一般にUFを100とするが、生体にとって異物とはいえない栄養成分について、食品添加物、農薬などと同じ観点でUFの値を設定する事の是非が問題になる。

$$UL = \frac{NOAEL}{UF}$$

食品成分の多くは、過去あるいは他地域において、食品として安全に使用されていた、もしくは使用されている歴史的もしくは経験的知見をもっている。これらの摂取知見を安全性評価に向けてどのように利用すべきかを考慮する必要がある。特に、それらの物質が過去もしくは他地域において摂取されていた、あるいは摂取されている条件と現時点で予定している使用条件との比較が安全性評価の要点となる。

A Considerations for Evaluating the Safety of Food Ingredients and Materials

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The safety of any substance including food ingredients or materials is evaluated on the basis of results from the risk assessment on the substance. Risk assessment is the use of available scientific information to characterize potential of adverse effects associated with exposure of humans to a substance under known or expected conditions. Methodologically, it consists of four steps, namely, hazard identification, hazard characterization, exposure assessment and risk characterization. Practically, risk assessment is intended to provide the scientifically sound basis for regulatory or non regulatory action to manage the risk in humans from the substance. Therefore, the final goal of risk assessment for supplementary use of certain food ingredient or material is to provide scientific evidence and scientific logic for the establishment of tolerable upper intake level (UL) for the substance.

The UL, a terminology corresponding to the acceptable daily intake (ADI) for food additives, refers to the highest level of a daily nutrient intake that is likely to pose no risk of adverse effects to almost all individual in the general population.

As in the case of an ADI for a food additive, a UL for a micronutrient is calculated on the basis of the No-Observed-Adverse-Effect- Level (NOAEL) in toxicological studies by applying an uncertainty factor (UF).

$$UL = \frac{NOAEL}{UF}$$

Traditionally, a 100 has been used as the standard value of UFs for food-related substances including food-additives, pesticide residues, micronutrients. However, it is necessary to device scientific methods or logic for establishing UFs of macronutrients.

Different from cases of food additives or agrochemical residues, no specific regulation has been applied to marketing of foods or food ingredients in Japan. This is derived from an empirical consideration that the safety of food ingredients or materials can be assured on the basis of accumulated historical or empirical evidence of safe use as foods. In association with a rapid progress of food science, expansion of foreign free trade and diversity of eating habit, however, various foods or food ingredients without sufficient historical evidence of safe use are now being increasingly introduced into our daily life. As a measure to solve this issue, in 2004 the Ministry of Health, Labour and Welfare amended the Food Sanitation Law. From the scientific point of view, it is necessary to establish comprehensive guidelines of toxicity tests and human studies required to compensate for insufficiency in historical evidence of safe use and to assure safety of the substance as a food ingredient.

ビタミン類の摂取上限値の決定に至る根拠

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過剰摂取によって明らかな健康障害が発生することが知られているビタミンは、レチノール（ビタミンA）、エルゴカルシフェロール（ビタミンD）、コレカルシフェロール（ビタミンD）、α-トコフェロール（ビタミンE）、ピリドキシン（ビタミンB_6）、ニコチンアミド（ナイアシン）、ニコチン酸（ナイアシン）とプテロイルモノグルタミン酸（葉酸）である。

レチノールは、肝臓障害を指標にし、最低健康障害発現量を14mgレチノール当量/日とし、不確実性因子を5として上限量は3mgレチノール当量/日とした。

エルゴカルシフェロールとコレカルシフェロールは、高カルシウム血症を指標にし、健康障害非発現量を60μg/日とし、不確実性因子を1.2として、上限量を50μg/日とした。

α-トコフェロールは、出血作用を指標にし、健康障害非発現量を800mg/日とし、不確実性因子を1として上限量を800mg/日とした。

ピリドキシンは、感覚神経障害を指標にし、健康障害非発現量を300mg/日をとし、不確実性因子を5として、上限量を60mg/日とした。

ニコチンアミドとニコチン酸は、ともに肝機能低下を指標にした。ニコチンアミドの健康障害非発現量は3000mg/日、最低健康障害発現量1500mg/日である。ニコチン酸の健康障害非発現量は500mg/日、最低健康障害発現量は1000mg/日である。各々の不確実性因子を5として、ニコチンアミドの上限量を300mg/日、ニコチン酸の上限量を100mg/日とした。

プテロイルモノグルタミン酸を悪性貧血患者に大量投与（0.35～500mg/日）すると、神経障害などの悪影響が発生する。一方において、神経管閉鎖障害の発生および再発を予防するために、受胎前後の3か月間以上の間、0.36～5mg/日のプテロイルモノグルタミン酸が投与されているが、悪影響がみられたという報告はない。そこで、暫定的ではあるが、健康障害非発現量を5mg/日とし、不確実性因子を5として、上限量を1mg/日とした。

ビタミンK（フィロキノン、メナキノン）、ビタミンB1（チアミン塩酸塩）、ビタミンB_2（リボフラビン）、パントテン酸、ビオチン、ビタミンC（アスコルビン酸）には過剰摂取による明確な悪影響が認められていないので、上限量の策定を見送った。

Evidences to Decision of Tolerable Upper Intake Levels of Vitamins

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The vitamins to which clear health disturbances are generated by the excess intake are retinol (vitamin A), ergocalciferol (vitamin D), cholecalciferol (vitamin D), α-tocopherol (vitamin E), pyridoxine (vitamin B_6), nicotinamide (niacin), nicotinic acid (niacin), and pteroylmonoglutamic acid (folacin).

The liver injury was made an index of the adverse effect of retinol, LOAEL was assumed to be 14 mg/day. When an uncertainty factor (UF) was assumed to be 5, the tolerable upper intake level (UL) was assumed to be 3 mg.

The hypercalcemia was made an index of the adverse effects of ergocalciferol and cholecalciferol, each NOAEL was assumed to be 60μg/the day. When each UF was assumed to be 1.2, each UL was assumed to be 50μg.

The hemorrhage action was made an index of the adverse effect of α-tocopherol, the NOAEL was assumed to be 800mg/a day. When UF was assumed to be 1.0, the UL was assumed to be 800 mg.

The sensorineural defect was made an index of the adverse effect of pyridoxine, the NOAEL was assumed to be 300mg/day. When UF was assumed to be 5, the UL was assumed to be 60 mg.

Nicotinamide and nicotinic acid both made a decrease in liver function an index. In nicotinamide, the NOAEL was 1500 mg/day and the LOAEL was 3000 mg/day. In nicotinic acid, the NOAEL was 500 mg/day and the LOAEL was 1000 mg/day. Each UF was assumed to be 5, the UL of nicotinamide was assumed to be 300 mg, and the UL of the nicotinic acid was assumed to be 100mg.

The excess amount of pteroylmonoglutamic acid administration (0.35-500 mg/day) to the pernicious anemia patient caused a neuropathy etc. However, there is no report that the adverse effect was seen though the pteroylmonoglutamic acid administration of 0.36-5 mg/day for three months or more before and after conception to prevent occurring and relapsing of the neural tube defect. Then, the NOAEL was assumed to be 5 mg/day. When UF was assumed to be 5, the UL was assumed to be 1 mg.

Because a clear adverse effect by an excessive intake was not reported in vitamin K (phylloquinone, menaquinone) vitamin B1 (thiamin hydrochloride), vitamin B_2 (riboflavin), pantothenic acid, biotin, and vitamin C (ascorbic acid), the decision of UL was put off.

ミネラルの摂取量の設定

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ミネラルの許容上限摂取量の設定には様々な方法が考えられている。その一つが、食事からの摂取とサプリメントからの摂取を合わせた現行のミネラル摂取量を算定し、母集団の摂取量の平均値及び90パーセンタイル値を見積もる方法である。現行のミネラル摂取量とミネラルの安全性に関する文献値との比較に基づき、現行の高摂取量で毒性が生じる危険性はないと仮定すると、ミネラル摂取量調査のデータから求められた上限摂取量は安全であると結論できるであろう。別の許容上限摂取量の設定方法として、リスク評価の原理を安全な上限摂取量設定に応用する方法がある。米国医学研究所が採用しているこの方法では、用量反応性に関する毒性データ及び臨床データを評価することにより安全な摂取量を導出できる無毒性量（NOAEL）を設定する。安全な上限摂取量を設定するため様々な方法を議論し、各種方法の利点や欠点を紹介する。

Setting Levels for Minerals

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There are various possible approaches that can be taken to setting acceptable upper intake levels for minerals. One such approach is to calculate the current intakes of minerals from both the diet and supplement use and estimate the mean and 90th centile intakes across the population. Assuming current high intakes do not present a toxicological hazard based on comparing these intakes with literature pertaining to the safety of minerals, one could conclude that upper intake levels determined from survey intake data would be safe. An alternative approach is to apply the principles of risk assessment to establishing safe upper intake levels. This process, adopted by the Institute of Medicine in the U.S. involves the evaluation of dose response toxicological and clinical data to establish a no-observed-adverse-effect level (NOAEL) from which a safe intake can be derived. The various approaches to establishing safe upper intake levels will be discussed and the advantages and disadvantages of various methods will be presented.

特定保健用食品の安全性評価の考え方

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特定保健用食品制度の概要

平成13年4月より「保健機能食品」制度が発足した。保健機能食品は特定保健用食品と栄養機能食品から構成されている。この制度はこれまでの「食薬区分」などの規制を緩和し、食品に健康上の有効性をより広く表示できるようにしたものである。特定保健用食品はすでに平成3年に発足していたが、これまでは通常の食品形態に限定されていたものが、平成13年よりは錠剤やカプセルなどの医薬品的な形状も認められるようになった。

特定保健用食品は関与成分といわれる有効成分を含む食品毎に審査されるシステムをとっているので、個別審査型が原則である。現在審査は有効性に関しては、厚生労働省薬事・食品衛生審議会が、安全性評価は食品安全委員会で行われている。

現在、保健の用途は栄養政策や健康政策に合致したものであることが求められる。これは、食品の形態や組成に対する審査においても栄養上や健康上望ましいものであるかが問われることになる。

安全性評価における基本的な考え方

安全性評価に関する資料作成では、食経験、*in vitro* 及び動物を用いた*in vivo*試験等、ヒト試験などが必要である。最近の安全生評価における傾向をみると次のようにまとめられる。

1. 食経験がとくに重視される。
2. ヒト試験では、プラセボを置いた二重盲検法により統計学的有意差、健常者、疾病予備軍、臨床検査値高値者での安全性確認、継続摂取、過剰摂取による安全性確認などが必要である。
3. 錠剤、カプセル、エキス、粉末などの医薬品的形態の食品では過剰摂取の安全性確認が重視される
4. 患者が摂取した場合、薬剤との併用、高齢者や妊産婦などが摂取した場合の安全性が重視され、注意喚起の表示が求められることがある。

Basic Principles for Safety of "Foods for Specified Health Use"

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Outline of "Foods for Specified Health Uses (FOSHU)"

On April in 2001, Foods with Health Claims established by the Minister of Health, Labor and Welfare (MHWL) and labeled with certain nutritional or health functions. This regulatory system for functional foods, FOSHU, has come into existence mainly from relief of difference between drugs and foods and to approve labeling statements regarding the effects of foods on human body. FOSHU has already established in 1991 and the regulatory range has broadened in 2001 to accept the forms of capsules and tablets in addition to those of conventional foods.

FOSHU refers to foods containing ingredient with functions for health and officially approved to claim its physiological effects of individual foods on human body. Food products applying for approval of FOSHU are scientifically evaluated in terms of their effectiveness by the Council of Pharmaceutical Affairs and Food Hygiene under the MHLW and in terms of their safety by Food Safety Commission.

FOSHU includes health functions that can positive effects on human physiological functions, and the related foods are intended to be consumed for maintenance or promotion of health or special health uses by peoples who wish to control their health conditions.

Basic concepts for evaluation of safety of FOSHU

Concerning the documentation of safety, consumption experience, both in vitro and in vivo studies and data by human studies are required. The points in recent evaluations are follows:

1. Consumption experiences are especially important.
2. The human studies should be performed basically by the placebo-controlled, double blind design and evaluated by the significant results. The safety should be also confirmed in the normal and borderline subjects and/or the subjects with high clinical data in the chronic intake and the excess intake,
3. The foods with the drug-like forms such as tablets, capsules, extract and powder are strictly evaluated.
4. As the interaction with drugs in the patients and the safety in the elderly parsons and the pregnant women are especially important, some warning notes are attached.

ポリフェノール類の一日摂取許容量の考え方

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野菜・果物・茶類に含まれるポリフェノールはヒトの健康を増進する効果があると考えられている。しかし、ポリフェノールは非栄養素である。その摂取量には上限値があるはずである。ここでは、その上限値を推定するための考え方を提案したい。大前提は、議論するポリフェノールがあくまで十分に長い食経験がある食事成分であるということである。ポリフェノールのほとんどが顕著な細胞毒性を示す。しかし、十分に長い食経験がある食事ポリフェノールは、小腸吸収時に速やかにグルクロン酸あるいは硫酸抱合を受ける。抱合体は排泄形態なのでそのほとんどが管腔に排泄される。ごく少量が血流を循環するが、1.5から23時間ほどの半減期で尿に排泄される。この尿への排泄速度は、他の食品成分と比べるときわめて速い。したがって、食事ポリフェノールが体内に蓄積されて毒性を示すとは考えにくい。実際にポリフェノールの単品をヒトが1ヶ月摂取した報告がいくつかあるが、それによると一日200 mgまでは悪影響は認められていない。一方、ヒトの食品中のポリフェノールは一種類ではなく複数の混在である。複数のポリフェノールが混在する場合には、その一部が抱合を逃れ、結果として毒性を示すものがあるかもしれない。しかしヒトは複数のポリフェノールを野菜などから日々摂取しているが、何らかの悪影響を感じることはない。したがって混合系でもポリフェノールが毒性を示すことはないと思われる。残る疑問は、多量に摂取したときに、消化管表面細胞に高濃度で作用して毒性を示すことはないか、である。この点を試験した報告はほとんどない。日常生活ではヒトは多量の野菜や果物を食べることがある。植物はポリフェノールと同時に食物繊維などを含んでいる。消化管内で、食物繊維はポリフェノールが消化管表面細胞に作用するのを阻害し、ポリフェノールの毒性発現を抑えると思われる。このように考えると、ポリフェノールの摂取上限値は、それを野菜などから摂るのならば、植物に含まれている量の範囲ならば問題はない。しかし、サプリメントとして摂るのならば、その摂取上限値をそのポリフェノールごとに毒性学的に試験し明確にして公表すべきであると結論できる。

A Way of Thinking for Allowance of Daily Intake of Dietary Polyphenols

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Polyphenols in vegetables, fruits and teas have been believed to exhibit beneficial effects on human health. The polyphenols, however, are non-nutrients for humans and should be estimated in an upper limit for daily intake allowance. Here I attempt to suggest the amounts of upper limit for dietary polyphenols intakes. Since most of polyphenols possess a strong cytotoxicity, the first prerequisite is "dietary", which means the polyphenols must have a long period of dietary experience as one of ingredients in human food. Polyphenols which have not been experienced or only been experienced for a short-period of time in human food, must be tested for the safety of the consumers, as well as food additives. Dietary polyphenols, however, immediately undergo conjugations with glucuronide and/or sulfate in intestinal cells during absorption process. It has been found that the conjugates are mostly excreted to the digestive lumen and fail to produce toxicity. A small part of the conjugates circulates in the blood stream and is excreted through urine with a half life of 1.5-23 h. The elimination times are very rapid compared to other food factors, indicating that dietary polyphenols are difficult to accumulate and produce toxicity. Several data tested the toxicity in humans indicated that less than 200 mg/day/capita of single species of polyphenols did not produced any side effects for 1-month ingestion. On the other hand, a mixture of various kinds of polyphenols may fail in the intestinal conjugations, and a part of dietary polyphenols escaped the conjugations may produce toxicity. Humans daily ingest the mixture of polyphenols in vegetables, and did not show any signs of abnormality, indicating that the mixed polyphenols do not cause side effects. A remaining question is the toxicity in the digestive tract by an excess amount of polyphenols when ingested. There is not enough information to evaluate the toxicity, but we know well that a large amount of vegetables gives no adverse effects. In plants polyphenols coexist with various components such as dietary fiber. The fiber probably intercepts the interaction of polyphenols with epithelial cells and mitigates the production of toxicity of polyphenols in the digestive tract. It can be concluded that dietary polyphenols at the levels in daily vegetables express no adverse effects, but the allowance of daily intake must be toxicologically made clear when the polyphenols are used as a supplement.

栄養素の安全な上限摂取量の設定に対する規制当局の考え方

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世界中の規制当局の担当者は、栄養素の安全な上限摂取量の設定プロセスに注目している。栄養補助食品、強化食品及び機能性食品の利用や交易が急速に広まる中で、その安全性の確保や国際的な基準の調和に注目が集まっている。

長年の間、規制当局は栄養素の安全な上限摂取量の設定にあまり注意を払っていなかった。上限値について取り扱う場合であっても、その栄養素の推奨摂取量を超えない量と規定される傾向にあった。時とともに、このような方法は科学的な厳密さを欠くと認識されるようになり、一部の人々は、特にリスク評価のプロセスを通じて、科学的根拠に基づいた安全な上限摂取量の決定方法の導入について主張し始めている。

国際レベルでは、ある種の栄養物質の最高1日摂取量をリスク評価により特定するという問題は、コーデックス委員会の作業の一環として高い注目を集めている。各国でもこの問題に取り組んでおり、1994年、全米科学アカデミーは、栄養物質の適正量に関する研究を拡大し、リスク評価モデルに基づく上限摂取量を設定することを含めると明言した。2000年までに、旧欧州委員会食品科学委員会（現欧州食品安全機関）はビタミン及びミネラルの許容上限摂取量設定のためのガイドライン（リスク評価法に基づくガイドライン）を制定している。他の国でも、ある種の栄養素の最大摂取量を設定しているが、多くの場合、基準値の決定プロセスは明確にされていないか、依然として推奨摂取量に基づいているようである。それにもかかわらず、栄養素のリスク評価は注目を集めている。最近では、日本健康食品規格協会が食品中のビタミン及びミネラルの最大量及び最小量の設定に関するコメントを出しており、その中でリスク評価を許容摂取量決定の基礎と見なしている。

このプレゼンテーションでは、栄養素の上限摂取量の設定に関する規制当局の政策決定の科学的根拠を確立するための取り組みについて概観する。ここでの議論は、規制当局の枠組みは国ごとに異なり、各国はその国独自の保護レベルを決定する権利を有するという認識に基づいている。しかし、どのような規制方針があったとしても、独立した組織による科学的審査が透明性のある方法で系統的に実施されることで情報が得られれば、全ての規制制度は最適に機能し、国際的な調和策がまとめられる可能性が高まることであろう。

A Regulatory Standpoint for Establishing Upper Levels of Safe Intake for Nutrients

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Regulatory officials world-wide are paying attention to the process for establishing the safe upper level of intake for nutrient substances. Rapidly expanding use of and trade in dietary supplements, fortified foods and functional foods have focused attention on both ensuring their safety and harmonizing standards internationally.

For many years establishing safe upper levels of intake for nutrient substances received little attention from regulators. To the extent upper levels were addressed at all, they tended to be specified as a level no higher than the recommended intake for the nutrient substance. Over time it was recognized that such an approach lacked scientific rigor. Some began to advocate for the identification of a science-based approach for determining safe upper levels of intake, most notably through the process of risk assessment.

On the international level, the issue of identifying maximum levels of daily intake for certain nutrient substances via risk assessment has received considerable attention as part of the Codex Alimentarius work. It has also been addressed regionally. In 1994 the US National Academies of Science specified that their studies of adequate levels of nutrient substances would be expanded to include specification of upper levels of intake based on a risk assessment model. By 2000 the former Scientific Committee on Food of the European Commission (now encompassed by the European Food Safety Authority) had established guidelines for development of tolerable upper intake levels of vitamins and minerals, guidelines based on risk assessment approaches. In other parts of the world, maximum levels for the intake of certain nutrient substances have been identified but in many cases the process for determining such standards have not been clearly identified or apparently continue to be based on the levels of recommended intakes. Nonetheless, nutrient risk assessment is receiving attention. Recently the Japanese Institute for Health Food Standards made available comments concerning the setting of maximum and minimum amounts of vitamins and minerals in foodstuffs which identified risk analysis as the basis for such tolerable intake determinations.

This presentation will overview the efforts to establish a scientific basis for regulatory decision-making regarding the establishment of upper levels of intake for nutrient substances. The context for the discussion is the recognition that regulatory frameworks vary from country to country – and that countries retain their right to determine their own level of protection. However, no matter what the regulatory policies, all regulatory systems operate most appropriately and are more likely to converge toward harmonization if they are informed by independent organized scientific reviews conducted systematically in a transparent manner.

許容上限摂取量（UL）に対する業界の見解―発展させた評価法のビタミン、ミネラル、生理活性物質およびアミノ酸への応用

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最初のUL法により、栄養素の安全性の評価に対するリスク評価の適合性は大きく改善したが、いくつかの欠点があるため、科学上のあるいは規制上の誤解が生じている。大量摂取による危険性がデータで立証されていなければ、ULは設定されない。ビタミンB12の場合、いかなる摂取量でも危険性は確認されておらず、データベースには食物からの通常摂取量の何千倍もの摂取量までの豊富なデータがあるが、ULが設定されていないために、ビタミンB12の抑制策が正当化されてきた。このようにULが設定されていないことによる誤解を防ぐため、新たに「どの摂取量においても副作用が確認されておらず、安全性に関する確かなエビデンスを有する最高摂取量」として「観察された安全量（OSL）」という概念が定義された。最近では国連食糧農業機関／世界保健機関（FAO/WHO）の報告書において、「観察された最高摂取量（HOI）」に同様の定義が与えられている。従前の研究方法に勝るUL法の大きな利点はデータベースに特有の不確実係数（UF）が適用できることであるが、その不確実係数の値が定量的に任意に見えることが不利ではある。米国医学研究所食品栄養審議会（IOM FNB）は、ヒトのデータセットに不確実係数1～5を、動物のデータセットに複合不確実係数36を選択した。不確実性を補正する際の客観性を高めるために、リスク評価は入手可能な臨床介入研究データの利用のみに制限し、その上で、1日摂取量の高い順にデータを配列し、各試験のデータの量及び質の評価を行い、不確実性について更に補正する必要がないように、十分条件を満たす試験の中で副作用が認められなくなるデータを高摂取量から低摂取量の順に検討していく。（すなわち、データを検討した結果、UF=1となる。）こうすることで、設定されたNOAELの値がULと等しくなる。言い換えれば、確認されたOSL値は不確実性の補正を必要としないのである。1回の試験に決定的な意味を持たせ、その単回の試験の証拠の力で不確実性を判断するというのではなく、この不確実性に対する新たな対処法では、確認されたNOAEL又はOSLに信頼性を置く。その理由はデータセットの質の高さだけでなく、高摂取量でも副作用が生じなかった試験が存在するところにある。OSL法とこの改善された不確実性評価法は、既に公開されている一連のリスク評価（カルニチン、コンドロイチン、コエンザイムQ10、クレアチン、グルコサミン、ルテイン及びリコピン）に活用されてきたが、既公開のビタミンDのリスク評価においても不確実性評価法が適用され、非常に高い値のULが新たに提唱されている。この不確実性に対する対処法は、多段階の用量が設定されている複数の臨床試験を含むどのようなデータセットにも応用できる。大半のアミノ酸をサプリメントとして摂取する場合、大量摂取と明確に関連する副作用は立証されていない。OSL法では、いくつかのアミノ酸の安全摂取量の推定が可能である。リスク評価により、既に臨床試験データからアルギニン、グルタミン及びタウリンのOSL値が確認されている。他のアミノ酸のOSL値を確認するため、リスク評価は現在も続けられている。

Industry Views of UL – Application of Expanded Method to Vitamins, Minerals, Bioactive Substances, and Amino Acids

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The original UL method greatly improved the application of risk assessment to the evaluation of safety of nutrients, but some shortcomings have led to scientific and regulatory misinterpretations. No UL is set where the data to not establish a *hazard* resulting from high intakes. This absence of a UL has been used to justify restrictive policies for vitamin B12, even though no hazard has been identified at any intake and the database is quite robust up to amounts thousands of times higher than usual intakes from food. To prevent such misinterpretation of the absence of a UL, the Observed Safe Level (OSL) was defined as "the highest intake with convincing evidence of safety, even if there are no established adverse effects at any level." Recently, a FAO/WHO report gave a similar definition to the Highest Observed Intake (HOI). A major advantage of the UL method over previous approaches is the application of database-specific Uncertainty Factors (UF), but a disadvantage is that the specific values seem quantitatively arbitrary. The IOM FNB selected UF values from 1 to 5 to human datasets and a composite value of 36 to an animal dataset. To improve the objectivity of adjustments for uncertainty, risk assessment can be restricted to utilize only clinical interventional trial data when available, with the data arranged in decreasing order of daily intake, evaluation of each trial for quantity and quality of data, and selection downward until no adverse effects are observed in a trial of sufficient quality to justify no further correction for uncertainty (i.e., selection of data so that UF = 1). Thus, the NOAEL selected is the UL, or the OSL identified requires no adjustment for uncertainty. Instead of identifying a single *critical study* and judging uncertainty on the strength of this single study, this new approach to uncertainty provides confidence in the NOAEL or OSL identified not only because of the quality of that dataset but also due to the existence of studies at higher intakes that also produced no adverse effects. The OSL method and the improved evaluation of uncertainty have been applied in a series of published risk assessments (carnitine, chondroitin, coenzyme Q10, creatine, glucosamine, lutein, and lycopene), and the uncertainty technique was applied in a published risk assessment of vitamin D that proposed a new, much higher UL. This approach to uncertainty can be applied to any dataset that contains multiple clinical trials at a variety of dosage levels. For supplemental intakes of most amino acids, no adverse effects that are clearly related to high intakes have been established. The OSL technique allows estimates of safe levels of intake for several of the amino acids. Risk assessments have identified OSL values from clinical trial data for arginine, glutamine, and taurine. Risk assessments are being performed to identify OSL values for several other amino acids.

現行データからアミノ酸の安全な上限摂取量を設定するための検討事項：アミノ酸摂取量の上限を定義する方法

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アルバータ大学農業食品・栄養科学科

ヒトのアミノ酸摂取量の上限に関する既存データは、基本的に観察、すなわち、どのくらい摂取してどのような副作用が生じるか、に基づくものである。ヒトにタンパク質結合アミノ酸と遊離アミノ酸を高用量で投与してその作用を比較する試験が多数行われている。これらの試験結果から、タンパク質結合アミノ酸は被験アミノ酸の血漿中濃度に与える影響がはるかに少ないことが認められている。これは、タンパク質を摂取すると、増加したアミノ酸摂取量の別の受け皿としてのタンパク質合成が刺激されるためである。実際には、アミノ酸の最大摂取は遊離アミノ酸のサプリメントとしての摂取によるものであって、アミノ酸が練習や試合での成績に良い効果をもたらすと信じているアスリートたちが摂取している。

以前、子ブタを用いた試験において、我々はフェニルアラニンの酸化率が最大となる摂取量を明らかにした。この量を超えると血漿中フェニルアラニン濃度は指数関数的に上昇した。我々は、アミノ酸の最大代謝（酸化）率を、上限摂取量の代謝マーカーと考えている。最近、他の研究者がラットにおけるロイシンの最大酸化率についても同様の現象がみられることを実証している。これらの実験データから、さらにはこの分野のヒトにおける公表データが少ないことからも、系統的な方法を用いて食品中の必須アミノ酸やヒトが過剰摂取している他のアミノ酸の最大酸化率を求める必要があると思われる。これにより食物アミノ酸の許容上限値を定義するための合理的根拠が得られると、我々は考えている。しかし、トレオニンなど一部のアミノ酸では、複数の代謝経路があるため、最大酸化率の決定法がより複雑になることは銘記すべきである。この場合、上限値の定義もさらに複雑になる可能性がある。

Considerations for Safe Upper Limits of Amino Acids from Current Data - An Approach to Defining the Upper Limits of Amino Acid Intake -

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The existing data on the upper limits of amino acid intake in humans is essentially observational; how much do individuals ingest and what side effects do they have. There are numerous studies in humans comparing the effects of high doses of amino acid given as protein bound versus as free amino acids. These studies have shown that protein bound amino acids have much less effect on plasma levels of the test amino acid, since protein intake stimulates protein synthesis as another sink for the increased amino acid intake. In practice the highest amino acid intakes are as free amino acid supplements and are ingested by athletes who believe the amino acids will give them a benefit in training and/or performance.

Previously in a piglet study we were able to define the point at which maximal phenylalanine oxidation occurred, above which plasma phenylalanine rose exponentially. We regard this value of maximal disposal (oxidation) of an amino acid as a metabolic marker of the upper limit of requirement. Recently others have demonstrated a similar maximal oxidation rate for leucine in rats. Based on these experimental data and the paucity of published human data in the field we feel that a systematic approach needs to be undertaken to define the maximal oxidation rate for all dietary indispensable amino acids, and other amino acids which are being ingested in excess by humans. We believe that this will provide a rational basis to define the upper limits of tolerance for dietary amino acids. However it must be remembered that some amino acids such as threonine are more complex since they have more than one route of disposal. In which case defining upper limits may be more complex.

アミノ酸過剰のバイオマーカー候補物質

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化学物質の暴露に対する安全性評価には、動物実験などにより求められた最大無影響量（NOAEL）に、種差や個体差を考慮した不確定係数をかけるという手法がとられる。実験動物からヒトへの外挿には、通常、不確定係数として100が用いられる。この係数の妥当性は種々の化学物質について示されているが、アミノ酸をはじめとする栄養素の安全性評価にこの安全係数を使用することは出来ない。例えばグリシンの一日許容摂取量を、安全係数100を用いて求めると、日本人が一日に摂取するグリシン量の平均値にも満たない数値になってしまう。この様な背景の下、栄養素を主成分とするサプリメントのリスク評価では、想定される摂取量が安全であることを、実際にヒトで評価することに重点が置かれる。しかしながら、栄養素の一日許容摂取量や上限摂取量を推定するためにヒト試験を実施することは、現実性に欠ける。なぜならば、個々のアミノ酸を悪影響が発現するまで投与するようなヒト試験を実施することは、倫理的な理由で困難だからである。ヒトにおける栄養素摂取のリスク評価には、ヒト試験にも適用可能、かつ、毒性変化を予想し得るバイオマーカーが必要と考えられる。

我々は、アミノ酸の上限摂取量の評価に向けて、2つのアプローチを提案している。一つは、アミノ酸過剰摂取による毒性変化の原因となる「毒性物質」、あるいは毒性を予見し得るバイオマーカーを実験動物を用いて同定する試みである。過剰量のアミノ酸摂取は、そのアミノ酸の正常代謝経路あるいは異常代謝経路の代謝物の体内蓄積に繋がると考えられ、それら代謝物がアミノ酸過剰毒性の発現に直接的あるいは間接的に関与する可能性が考えられる。もう一つのアプローチは、要求量以上に摂取したアミノ酸の「代謝限界」を見出す試みである。動物やヒトは、蛋白やアミノ酸摂取量の変動に対して、酵素活性調節等を介して適応する能力を持っている。従って、代謝限界を超えない摂取量が安全な摂取量である可能性が考えられる。

そこで、これらアプローチがラットにおけるアミノ酸の上限摂取量推定に活用出来るか否か、メチオニンとロイシンをモデルケースとして検討した。メチオニンは比較的低用量の摂取で成長抑制をはじめとする悪影響を及ぼすが、ロイシンは比較的大量に摂取しても悪影響の見られないことが知られている。ラットに種々の用量のメチオニンもしくはロイシンを添加した飼料を摂取させ、血漿中の代謝物をGCMSやアミノ酸アナライザー等を用いて網羅的に分析した。検出された代謝物と毒性変化の相互関係を解析し、メチオニン過剰摂取のバイオマーカー候補として、血漿中のメチオニン自体及びホモシステイン等の代謝物が抽出され、また、ロイシン過剰摂取のバイオマーカー候補として血漿中ロイシン及びαケトイソカプロン酸が抽出された。次に、メチオニン及びロイシンの代謝限界の有無を検討した。種々用量のメチオニン添加食を摂取させた動物の血漿メチオニン濃度とメチオニン摂取量の間に二相性の関係が見られた。ロイシン添加食を摂取させた動物の血漿ロイシン濃度とロイシン酸化速度の間にも二相性の関係が見られた。これら二相性の関係は、これらアミノ酸の代謝に限界のあること、つまり二相性の関係における折点以上の摂取量が代謝許容量を超えていることを示唆している。折点における摂取量は、NOAEL以下であり安全な摂取量であった。毒性のバイオマーカー候補として抽出された代謝物が、同時に代謝限界を評価する上でのバイオマーカーであったことになる。これら代謝物の、メチオニン及びロイシン過剰毒性への関与についてさらに議論したい。

Possible Biomarkers for Amino Acid Excess Determination

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Classic risk assessment of non-nutrient is based on determination of no observed adverse effect levels (NOAELs) and application of uncertainty factors (UFs). Normally, an UF of 100 is applied to a NOAEL to extrapolate animal data to humans for the risk assessment of chemicals. Although the use of the UF of 100 has been reviewed and validated, their routine application in the risk assessment of nutrients is not possible. If an UF of 100 is applied to amino acids, for example in case of glycine, we have shown that the calculated acceptable daily intake (ADI) would be lower than the average intake of glycine in Japanese. Against this backdrop, the current safety evaluation of nutritional food supplements places great emphasis on clinical data for humans. However, direct determination of NOAEL in humans to estimate ADI or upper intake level lacks reality, because of the difficulty in identifying hazardous changes caused by excessive intake of individual amino acids in human due to ethical reasons. Therefore, certain biomarkers, which can predict toxic changes and are applicable to human studies, would be necessary for nutrient risk assessment.

We have proposed two approaches that may be useful in determining the upper adequacy range for amino acids. One approach is to attempt to identify "toxic metabolites" that were responsible for toxicity or biomarkers for the toxicity of excessive intake of an amino acid in rats. Excessive intake of an amino acid could result in accumulation of the amino acid or its downstream metabolites in the normal or certain abnormal catabolic pathways, which could be involved in toxicities either directly or indirectly. Another approach is to try to identify "metabolic upper limits" in the catabolic pathways. Both animals and humans have ability to adapt to various dietary intake levels of protein and amino acids by controlling enzymatic activities. Thus, intake levels within the "metabolic upper limits" could be safe.

We tested whether these two approaches work for risk assessment of methionine and leucine in rats as model cases. Methionine is known to affect adversely for growth at lowest dose, while leucine is not associated with adverse effects at the same dose. At first, we profiled plasma metabolites of rats given various dosages of additional methionine or leucine dietarily, using GCMS, amino acid analyzer and so on. By analyzing correlations between these metabolites detected and toxicity endpoints, we identified methionine and its downstream metabolites such as homocysteine as biomarker candidates for methionine excess, and leucine and α-ketoisocaproic acid as biomarker candidates for leucine excess. Next, we investigated the existence of "metabolic upper limits" in rats fed excessive methionine or leucine. As a result, we found a breakpoint in the relation between concentrations of plasma methionine and intake levels of methionine. We also found a breakpoint in the relation between plasma leucine concentrations and rates of leucine oxidation. Both of the relations indicate existence of certain "metabolic upper limits", i.e. overloading of these amino acids above the intake levels at the breakpoints. Intake levels of both methionine and leucine below the breakpoints were safe levels, which were less than or equal to the NOAELs of these amino acids in rats. It was of interest that some of the metabolites determined as biomarker candidates for toxicities were identical to the biomarkers to assess "metabolic upper limits." Possible involvements of these metabolites in toxicities of excessive methionine and leucine will be discussed further.

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