出國報告（出國類別：進修）

# 美國波士頓大學醫學研究所
# 醫療營養學碩士


服務機關：衛生署台南醫院
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出國期間：100-07-15~101-06-25
報告日期：101-09-17

Boston Medical Center (波士頓醫學中心)_波士頓大學醫學院研究所以及教學醫院所組成，是美東重要的醫學重鎮之一。

摘要

本人為遴派「100 年度行政院衛生署所屬醫院醫事人員出國計畫」進修人員，於民國 100 年 7 月 15 日起為期一年，在美國波士頓醫學中心進修並取得醫療營養碩士學位，該研究機構為美國糖尿病與肥胖的研究重鎮。糖尿病在台灣地區的發生率約 6%。雖說良好的血糖控制可有效地降低因糖尿病所引起的併發症，但無論運動、飲食、行為調整、降血糖藥物及施打胰島素等方法，都無法治癒該病症。

第二型糖尿病患同時有嚴重肥胖的問題。研究顯示，肥胖會導致身體對胰島素產生抗性，當病患肥胖程度越嚴重，血糖就越難控制。因此肥胖型的糖尿病患者，最有效的治療方式是降低體重。最近國際頂尖的外科醫學雜誌不約而同提出胃腸道繞道減肥手術能治癒90%以上的肥胖糖尿病患，而不再需要藥物。這些病患術後不論血糖、血液中胰島素的含量及糖化血紅素的數值皆恢復正常。血糖狀況最長的追蹤時期達14年，而未見復發。

糖尿病與外科病患之術前評估以及預後密不可分，本人身為消化系外科專科醫師，因此，對此領域非常有興趣。自民國100年7月舉家前往美國波士頓進行醫療營養進修之旅。

波士頓大學醫療營養碩士的五個核心領域課程的工作包括:

1. **Molecular, Biochemical and Physiological Bases of Nutrition I&II: Energy, Vitamins and Minerals**
2. **Clinical and Public Policy Applications in Medical Nutrition Sciences**
3. **Medical Nutrition Sciences Seminar**
4. **Nutritional Epidemiology**
5. **Master's Thesis**

本文中將敘述每個課程的目的、過程、參與的活動及本人的論文報告和口頭報告和心得。

目次

## 目的

身為一般外科醫師，尤其專攻腸胃道手術，特別需要臨床及基礎營養醫學的知識，其內容重點，已由三十多年前的營養支持，二十多年前的營養產品全面化，十多年前的營養免疫調控，進步到今日的藥物營養學、分子營養學，乃至基因營養學等。不僅在台灣抑或是美國，醫學院以及外科住院醫師的訓練都鮮少於這一領域的研究以及探討。主要是基於醫學院訓練過於偏向藥理的機制與應用，但基礎營養代謝生理課程比例明顯不足以至於未被重視。但其臨床之重要性不可言喻，尤其許多疾病已經被證明與營養失衡相關，糖尿病以及肥胖更是現今文明病之首。

本人此次前往波士頓醫學院進修醫療營養學之主要目的為，經由完整的生理以及分子學知識來學習營養在生理學上所扮演的角色。並且透過臨床 Nutrition Support Team 的實習來連結臨床上的應用。尤其著重在外科病患腸道及靜脈營養的治療與研究。在新醫療技術的學習方面，由於近年來發現針對第二型糖尿病的治療，減肥手術中的胃繞道手術被證實在血糖控制甚至血酯代謝療效遠勝於傳統藥物治療。波士頓醫學中心為此相關研究的重要機構。因此此次進修另一重要目的即是學習且參與波士頓醫學中心此一研究，並將新技術以及新知識帶回台灣，以造福台灣糖尿病的患者。

營養學之分子生化以及生理基礎 **I &II: 能量, 維他命以及礦物質 (Molecular, Biochemical and Physiological Bases of Nutrition I &II: Energy, Vitamins and Minerals)**

目的**:** 學習人體能量攝取以及營養代謝過程的生理機制以及分子生化

**(**Concepts of essential nutrients and methods for determining their requirements (DRIs), body composition, nutrition and growth, energy expenditure, vitamins and mineral metabolism, functions and roles in signaling from gene to whole organism. Implications for nutrient requirements through the life cycle and in health and disease will be discussed.)

過程

**READINGS**

**Suggested text: Biochemical, Physiological, & Molecular Aspects of Human Nutrition, Author: Stipanuk, 2nd Edition, 2006** (a copy is available in the library – other texts if you have them are probably OK – you can check with me – the purpose is for basic background reading)

**Additional Readings** (review articles and research papers) will be selected by lecturers and posted on Blackboard (blackboard.bu.edu). The readings from the literature will generally be from journals such as American Journal of Clinical Nutrition, Journal of Clinical Investigation, Journal of Clinical Endocrinology and Metabolism, JAMA, NEJM, Journal of Nutrition, Science, Nature). There will usually be weekly writing assignments on the readings.

**DISCUSSION & WRITING ASSIGNMENTS**

Most classes will include an 60-80 min. discussion of assigned papers that will emphasize critical thinking, key methods, and scientific writing skills. Weekly writing assignments will help you focus your ideas and improve your scientific writing skills. For each topic, a basic biology and a clinical/epidemiological paper will be selected from current literature and/or important 'classics'. These sessions will be moderated by the lecturer or other nutrition faculty. In some cases, an Instructor (Dr. Lee) or an advanced post-doc will help with smaller groups.

Examples of the Lecture.

## Nutrients

- **Macronutrients**
  **[Fat, Prot. (essential amino acids), Carb]**
- **Vitamins**
  - **organic compounds body can't synthesize**
  - **small amounts required in the diet**
  - **need for proper function**
    - **growth, metabolism, cellular integrity**
  - **don't oxidize for fuel, use for biochemical functions**
- **Minerals/Trace elements**
  - **inorganic – biochemical structural roles**
- **Other food components** that promote health:
  - fiber,
  - "non-essential" or conditionally essential nutrients
  - phytochemicals

- Vitamins
  - organic substances grouped together because we need to eat them
    - **for normal growth, reproduction, health**
    - but…. how about vitamin D, niacin?
      - dietary requirement depends on environment
  - No common structure, but classified as fat and water soluble
- Minerals
  - inorganic
  - macro (tend to concentrate in the skeleton)
  - micro
  - ultratrace

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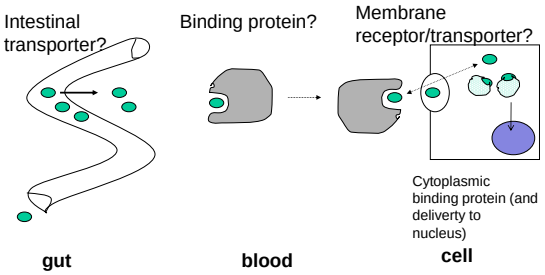
## How to understand nutrient requirements?

- Must understand function at various levels:
  - **physiological**
    - **at <u>whole body</u> level (e.g. absorption, digestion, interorgan transport, excretion)**
    - **<u>cellular</u> level: (transport into, around, and through cells)**
  - **biochemical** (co-factor function)
  - **molecular**
    - nutrient effects on gene expression

To fully understand nutrient requirements under given conditions, must understand the ***<u>mechanisms</u>*** underlying the utilization of that nutrient:
*e.g. absorption, transport to tissues/cells, to nucleus?*

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## What regulates intestinal <u>absorption</u> of a nutrient?

- Is it dependent on level of intake?
  - e.g. low or high calcium diet
- How does it cross the cell?
- Does it need require energy ?
- Does it need help?
  - Transporters to get across the cell membrane
  - Chaperones to get through the cytoplasm to where it is needed
  - what molecules are involved?
  - how are their levels regulated?
  - how is their function regulated?

## To determine nutrient requirements

1. Classic method Balance study
   - will tell you the intake that maintains pool size under given conditions
     - <u>problem</u>: requirements depend on pool size
       - is a large pool size necessarily better for health?
     - doesn't tell you how homeostasis is maintained
2. Turnover study with tracer methods
   - determine how fast nutrient is used and size of the body pool (s).

**醫療營養科學之臨床與公共政策之應用(Clinical and Public Policy Applications in Medical Nutrition Sciences)**

目的:

本課程將專注於營養和飲食有關的疾病狀態，並著重於臨床營養學的研究。
Goals and objectives: The course will focus on disease states related to nutrition and diet, with a major focus on clinical nutrition research by established investigators.

1. Acquaint students with current concepts and methods in clinical nutrition research.

2. Familiarize students with clinical research and how investigators approach nutrition-related questions in their specific fields to answer questions related to disease states.

3. Recognize the role of nutrition as it relates to major diseases, including cardiovascular, diabetes, gastrointestinal, osteoporosis, obesity, and cancer.

過程

| WEEK | TOPIC | ASSIGNMENTS | SPEAKER |
|---|---|---|---|
| January 19 | Folate and Cancer | | Joel Mason, MD |
| January 26 | Nutritional Therapies in the Prevention and Treatment of Osteoporosis | | Michael Holick, MD, PhD |
| February 2 | Diabetes Resolution After Bariatric Surgery | | Caroline Apovian, MD |
| February 9 | Calcium and Dairy Intake and Adolescent Health | | Lynn Moore, ScD |
| February 16 | Current controversies in parenteral nutrition | Assignment #1 due | Lorrie Young, RD, MSc |
| February 23 | The Role of Essential Fatty acids in Infant Development | | Megan Ruth, PhD |
| March 1 | Public Health Perspective on Childhood Obesity | | Alison Field, ScD |
| March 7 | MIDTERM EXAM 9am – 11am | | |

| | | | |
|---|---|---|---|
| March 8 | The metabolic consequences of visceral versus subcutaneous adipose tissue accumulation in obesity | | Caroline Fox, MD, MPH |
| March 15 | **NO CLASS – SPRING BREAK** | | |
| March 22 | Microbiome in Type 2 Diabetes | | Marie McDonnell, MD |
| March 29 | Omega-3 fatty acids and cardiovascular disease | Assignment #2 Due | Dariush Mozaffarian |
| April 5 | Protein Intake & Exercise Resistance Training in the Elderly | | Shalender Bhasin, MD |
| April 12 | The role of physical activity and exercise in preserving lean mass and mobility in the elderly | | Roger Fielding, PhD |
| April 19 | Sodium intake, hypertension and cardiovascular disease | | Nancy Cook, ScD |
| April 26 | Metabolic Consequences of carbohydrate overfeeding | Assignment #3 Due | Nawfal Istfan, MD, PhD |
| May 10 | **FINAL EXAM** | | |

**醫療營養學專題討論(Medical Nutrition Sciences Seminar)**

目的

針對研究主題，搜尋最新研究成果以及證據提出探討，我的主題為:
Metabolic Surgery to Treat Type 2 Diabetes: Clinical Outcomes and Mechanisms of Action

過程

我與我的指導教授
**Prof. Susan Fried & Prof. Lynn Moore**

# Metabolic Surgery to Treat Type 2 Diabetes:

# Clinical Outcomes and Mechanisms of Action

Presented By Jen-Pin Chuang

2012.05.03

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## Efficacy of different bariatric operations


| | LAGB | RYGB | BPD |
|---|---|---|---|
| Resolution of T2DM | 48% | 84% | 98% |
| Resolution of hypertension | 43% | 68% | 83% |
| Improvement of hyperlipidemia | 59% | 97% | 99% |
| % Excess weight loss | 47% | 62% | 70% |

***Level 1 clinical evidence to support surgery as an alternative treatment option is lacking !!***

*JAMA 2004 292:1724–37*
JAMA 2008; 299:316-23.
Am J Med 2009;122(3):248.e5-256.e5.

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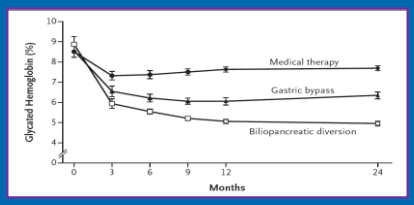
Bariatric surgery resulted in better glucose control than did medical therapy in T2DM obese Patients

N Engl J Med. 2012 Mar 26




**Weight-Independent Antidiabetes Effects (RR)**
- RYGB: **7.5** (95% CI,1.97 to 28.61; P<0.001)
- BPD: **9.5** (95% CI, 2.54 to 35.51; P<0.001)

as compared with the medical-therapy group.

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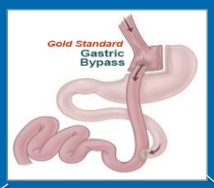
## WHAT IS THE MECHANISM BEHIND ??




**Rapid diabetes improvement** ??

??

**Significant Sustained Weight Loss** ??

Ann Surg 2003 238:467–484 Obesity (Silver Spring) 2008 16:298–305
Obes Surg 2005 15:474–481 Surg Obes Relat Dis 2009 5:346–351

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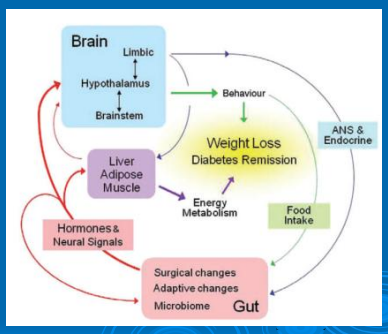
**Post RYGB leads to reduce food intake and**

Flow of information potentially involved in the physiological and behavioural consequences of gastric bypass surgery




obesity reviews (2011) 12, 984–994

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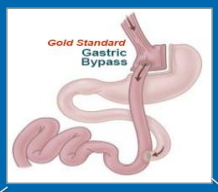
## WHAT IS THE MECHANISM BEHIND ??




**Rapid diabetes improvement**

??

??

**Significant Sustained Weight Loss**

- ✓Reduce FI
- ✓Decrease Fat and protein absorption
- ✓Increase EE

Ann Surg 2003 238:467–484 Obesity (Silver Spring) 2008 16:298–305
Obes Surg 2005 15:474–481 Surg Obes Relat Dis 2009 5:346–351

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## Proposed Weight-Independent Mechanisms of Diabetes Improvement after GI Surgery

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## The starvation

## The starvation-followed-by-weight-loss hypothesis

- Residual β-cells are only minimally challenged simply because eat less in the immediate postoperative period

- ✓ Diabetes remits in only 48% of LAGB cases, compared with 84% of cases after RYGB
- ✓ Glycemic control tends to worsen after major surgery due to inflammation and up-regulation of stress hormones
- ✓ Fails to explain the superiority of the glycemic control achieved after RYGB *vs. equivalent weight loss from dieting or restrictive bariatric* operations

Ann Surg 2005. 238:467–484; discussion 484–465
Obes Surg 2005. 15:474–481

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## The Early Effect of the Roux-en-Y Gastric Bypass on Hormones in Rat Model

Endocrinology, April 2010, 151(4):1588–1597

- Leptin↓ , Insulin↓, Glu ↓ after RYGB compared with sham group.

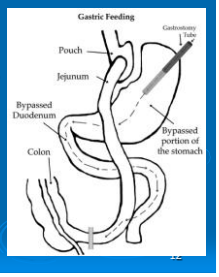
- **Post-RYGB Hormones Change**

| Hormones | Basal level | Post meal change | AUC | relationships between BW or BWL |
|---|---|---|---|---|
| GLP-1 | Twice ↑↑ | ↑↑ | ↑↑ | -∝BW |
| PYY | 3 folds↑↑ | ↑↑ | ↑↑ | -∝BW |
| GIP | →→ | →→ | →→ | – |
| Active Amylin | →→ | ↑↑ | ↑↑ | ∝BWL |
| Acylated Ghrelin | →→ | ↓ (Vs Sham) | ↓↓ | -∝BWL |

## Mechanisms of incretin release after gastric bypass: -Upper Intestinal Hypothesis-

- Nutrients are no longer in contact with the upper intestine

- ✓ *Less of **hypothetical antiincretin** is released*
- ✓ *Controversial results in gastrostomy tube feeding experiments.*




Curr Opin Endocrinol Diabetes Obes 2008;15:153–158
Diabetes Care 2008, 31(Suppl 2):S290–S296
*Am J Physiol Gastrointest Liver Physiol 2011, 300: G795–G802*

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## Mechanisms of incretin release after gastric bypass: -Lower Intestine Hypothesis-

- **Enhanced and accelerated delivery of unabsorbed food to from the Roux limb to ileum**

- ✓ GLP-1 ,PYY and oxyntomodulin, is produced primarily in the ileum and colon by nutrient-stimulated L cells
- ✓ Support for the lower intestinal hypothesis comes from experiments involving ileal interposition

Am J Physiol Endocrinol Metab 2005 288: E447–E453
Obes Surg 200515:1258–1264

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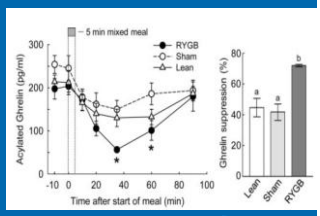
## The Ghrelin Hypothesis

90% of ghrelin is produced by the stomach and duodenum, tissues altered by RYGB

➢**Ghrelin**
✓Suppress adiponectin
✓Block hepatic insulin signaling at the level of PI3K
✓Inhibit insulin secretion

➢ In human, compromised secretion of the orexigenic, upper GI hormone ghrelin might contribute to the anorexic and antidiabetic effects of RYGB




N Engl J Med 2002 346:1623–1630

Endocrinology, April 2010, 151(4):1588–1597

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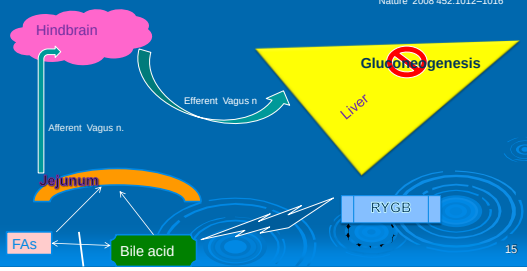
## Intestinal regulation of insulin sensitivity

- Activate a novel intestine-brain-liver neurocircuit to increase hepatic insulin sensitivity by intraduodenal infusion of lipids in rats.

Nature 2008 452:1012–1016

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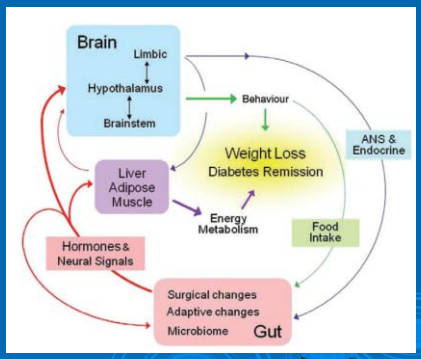
## Flow of information potentially involved in the physiological and behavioural consequences of gastric bypass surgery




obesity reviews (2011) 12, 984–994

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營養流行病學 **(Nutritional Epidemiology)**


目的: 經由流行病學的研究，提供醫療營養學完整的臨床證據。

過程:

| Session | Date | Topics | Speakers | Read from primary text prior to session |
|---|---|---|---|---|
| 1 | 9/12 | • Introduction and course logistics<br>• Overview of clinical research<br>• Developing the study question | Fish | Chapter 1<br>Chapter 2 |
| 2 | 9/19 | • Test qualities affecting study designs (accuracy, precision, sensitivity and specificity)<br>• Bias and confounding | LaMorte<br>McNair | Chapter 4 and 12 |
| 3 | 9/26 | • Selecting study population; inclusion criteria and recruitment considerations<br>• Cross sectional studies | Fish<br>McNair | Chapter 3<br>Chapter 8 (cross-sectional) |
| 4 | 10/3 | • Cohort Studies<br>• Baseline and outcome measures<br>• Review cross-sectional study article in class | Fish<br>McNair | Chapter 7 |
| 5 | 10/11 **(Tues)** | • Drug development research and FDA regulated studies<br>• Research Ethics and the role of an IRB | McNair<br>Fish | |
| 6 | 10/17 | • Case-control studies<br>• Group time to work on projects | Kaufman | Chapter 8 (case-control) |
| 8 | 10/31 | • Clinical Trials: Study rationale and Equipoise; special issues | Fish | Chapter 10<br>Chapter 11 |

| | | | | |
|---|---|---|---|---|
| | | with interventional studies<br>• Experimental Designs for Clinical Trials part 1 | Fish | |
| 9 | 11/7 | • Device research<br>• Experimental Designs for Clinical Trials part 2 | Aulwes<br>Fish | |
| 10 | 11/14 | • Calculation of sample size<br>• Methods of randomization<br>• Collecting safety data in clinical studies | Fish<br><br>McNair | Chapter 5<br>Chapter 6 |
| 11 | 11/21 | • Data monitoring committees and interim analyses<br>• Data analyses and analysis populations | Sankoh<br><br>Fish | |
| 12 | 11/28 | • Protocol discussion and IRB meeting video<br>• Responsible conduct of research | Fish | |
| 14 | 12/12 | **Presentations of study protocols to class** | | |
| 15 | 12/19 | **Presentations of study protocols to class** | | |

**Primary Textbook:** Designing Clinical Research (Third edition). Authors: Hulley, Cummings, Browner, et al. Lippincott, Williams & Wilkins, 2006. Additional readings and assignments are posted in the "Assignments" section of Blackboard.

**碩士論文(Master's Thesis)**

BOSTON UNIVERSITY

SCHOOL OF MEDICINE

Thesis

# LIPID RISK PROFILE IN DIFFERENT ETHNIC GROUPS AFTER ROUX-EN-Y GASTRIC BYPASS OPERATIONS FOR MORBID OBESITY

by

**JEN PIN CHUANG**

M.D., University of National Cheng Kung University, 2001

Submitted in partial fulfillment of the

requirements for the degree of

Master of Arts

2012

# LIPID RISK PROFILE IN DIFFERENT ETHNIC GROUPS AFTER ROUX-EN-Y GASTRIC BYPASS OPERATIONS FOR MORBID OBESITY

**JEN PIN CHUANG**

Boston University School of Medicine, 2012

**Major Professor: Nawfal Istfan, M.D., Ph.D., Associate Professor of Medicine**

ABSTRACT

**Background.** Bariatric surgery is currently the most effective treatment for severe obesity. Roux−en-Y gastric bypass (RYGB) has emerged as the surgical procedure of choice due to its favorable risk-benefit profile. It has also been reported to remit type 2 diabetes and to reduce rates of cardiovascular disease by lipid profile improvement. However, there are no longitudinal data that address lipid profiles in different ethnic groups following bariatric surgery. The goal of this study was to determine whether race/ethnicity affects reduction in lipid levels after Roux-en-Y gastric bypass operations.

**Methods.** Retrospective chart reviews were conducted for 913 consecutive obese patients undergoing gastric restrictive surgery in Boston Medical Center from 2004 to 2010. For these analyses, we included 825 patients consisting of 166 African Americans, 505 Caucasian Americans and 154 Hispanic Americans with 2 years of follow-up data. Mean levels for lipids and glycemic control were compared with ANOVA and longitudinal mixed linear modeling

**Results.** Baseline analysis revealed a hypertension prevalence in obese African American patients of 66.3%, significantly higher than that for Hispanic and Caucasian Americans ($p<.003$). Nevertheless, this group of patients appeared to have a more favorable lipid profile with higher baseline high density lipoprotein (HDL) and lower baseline triglyceride (TG) level compared with other racial groups.($p<.001$ and $p<.001$, respectively).

After RYGB, all obese subjects in three racial groups showed improvement in glycemic control and lipid profile over two years follow up. Multivariate analysis further demonstrated that two years after RYGB, African Americans showed significantly less improvement in HbA1C compared with white obese patients and Hispanic Americans ($p=.003$ and $p=.004$, respectively).

Lipid profiles appeared to be less favorable in whites than in African Americans. When other factors significantly affecting lipid levels were adjusted for in multivariate models, African Americans consistently maintained the lowest TG concentrations and highest HDL of three racial groups while the least favorable levels were observed in Caucasian Americans, even after adjusting for percent of maximal weight loss. For total cholesterol and LDL level, obese Hispanic American patients significantly improved in their first six months after operation. However, there was an obvious rebound in lipid levels starting eighteen months after RYGB, with Hispanic Americans having a higher level than African Americans ($p=.0021$) and Caucasians ($p=0.3498$) at 24 months after surgery.

**Conclusion**

After RYGB, among three major ethnic groups in United States, African American obese patients showed the poorest glycemic improvement but the most favorable improvement in lipid profile (i.e., decreased TG concentration, total cholesterol and LDL with a higher HDL) at the two-year follow up. Unlike African Americans, Hispanics and Caucasians were more resistant to lipid profile improvement. These significant differences in glycemic control and lipid profiles after RYGB in this ethnically-diverse group of obese patients suggest that it is critical to consider race/ethnicity in designing appropriate treatment modalities for obese patients undergoing gastric bypass surgery.

心得與建議

我和內人李妍蒨醫師有幸能同時得到衛生署獎學金，全家一起在波士頓生活以及學習一年，我們夫妻倆除了開拓國際視野，學習到許多新的醫療觀念與技術，我們三個小孩也體驗了麻塞諸塞州對兒童的照顧以及教育的重視。我的大兒子更得到劍橋市公立學校的科展 Curiosity Awards(全市僅有 22 人獲獎， 其中僅有三位亞洲人)，前往 MIT(麻省理工學院)領獎。感恩衛生署的栽培，也希冀政府能重視人才的培育，多提供在職人員更多以及更長時間出國進修的機會。


我的大兒子莊松岳於 MIT 領獎

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