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178

Gestational nutrition and the development of obesity during adulthood

Raghow R

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APPENDIX I Meetings
I-V Instructions to authors

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Gestational nutrition and the development of obesity during adulthood

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Abstract

Recent epidemiological studies indicate a strong link between intrauterine under-nutrition and propensity of such offspring for developing obesity and metabolic syndrome in later life. Garg *et al* investigated the mechanistic basis of this phenomenon and its potential reversibility in rats. The authors found that rats experiencing gestational under-nutrition but fed normally after birth (IUGR) gained body mass with excessive subcutaneous and visceral fat. The IUGR rats were also metabolically inflexible since they showed similar rates of energy expenditure and O₂ consumption in the fed and fasted states. However, if such pups were food-restricted during lactation (PNGR), their metabolic profiles resembled those of control and IPGR (subject to food restriction during pre- and postnatal periods) rats. Thus, postnatal caloric restriction superimposed on intrauterine under nutrition significantly improved insulin sensitivity and adiposity of rats that would otherwise develop metabolic inflexibility and visceral obesity. The observations of Garg *et al*, have serious implications in term of the design of the future experimental studies as well as their clinical translation in humans.

INVITED COMMENTARY ON HOT ARTICLES

Obesity and adult onset type 2-diabetes (T2DM) and their cardiovascular co-morbidities are rapidly becoming a global epidemic. According to the estimates of the World Health Organization, more than one billion people on earth are overweight and about one third of these individuals may be considered obese^[1]. Epidemiological observations indicate that the underlying causes of this massive increase in obesity and type T2DM worldwide are largely socio-economic in origin. However, the underlying mechanisms that predispose individuals to developing obesity-associated insulin resistance, hypertriglyceridemia, lower high-density lipoprotein/very low-density lipoprotein ratio, visceral adiposity and hypertension (the so called metabolic syndrome) may be quite different in different populations around the globe.

In the developed nations such as United States, the overarching causes of obesity and T2DM appear to be a prevalence of calories-rich fast food diet, overeating and lack of physical exercise. However, changes in life style (e.g., adoption of Western style diets) and physical inactivity, due to improved economic conditions, only partially explain the rise in the numbers of new cases

of T2DM and obesity in the developing countries. Recent epidemiological data strongly indicate that another key factor involved in the rise of this epidemic in many countries may be poor maternal nutrition during pregnancy. It has been appreciated for decades that intrauterine nutrition profoundly influences the developing fetus. For instance, undernourished mothers often give birth to babies weighing less than 2.5 kg, a much lower birth weight than their peer group^[2]. The rapidly emerging body of evidence suggests that poor intrauterine nutrition can also influence the incidence of metabolic and related health problems of the newborn during adulthood. The mechanistic basis of this link between intrauterine nutrition and propensity for obesity and metabolic syndrome in later life is poorly defined at present.

Barker *et al*^[3] were the first to recognize that intrauterine nutrition not only shapes the metabolic phenotype of the fetus but also its response to environmental conditions encountered after birth, and most likely throughout adolescence and adulthood. Since then, a number of epidemiological studies have shown that smaller sized human infants, resulting from intrauterine under nutrition, are more likely to acquire increased adiposity later in life^[4-7]. How does nutritional deprivation of a fetus predisposes it to become obese and to develop metabolic syndrome later in life remains a hotly pursued question, both in the laboratory and in the clinic.

The “thrifty genotype hypothesis”, originally proposed by Neel *et al*^[8], appears to be a dominant paradigm guiding much of the ongoing search for the mechanism to explain the relationship between intrauterine under nutrition and the propensity of the newborn for adiposity and T2DM during adolescence and adulthood^[9]. Fetal development is marked by extraordinary complexity and plasticity. According to the thrifty genotype hypothesis, exposure to gestational under nutrition triggers a thrifty gene(s) that reprograms the fetal muscle and adipose tissue to become insulin resistant in order to insure adequate supply of glucose in circulation needed for an optimal growth of the developing fetus^[9]. Experimental data from a number of species lend strong support for the concept that intrauterine exposure to under nutrition induces changes in the fetal insulin signaling pathways^[10]. It should be noted however that the molecular underpinnings of the thrifty genotype hypothesis remain rather sketchy since no gene(s) that determine metabolic reprogramming in response to nutritional deprivation of fetus and its propensity for obesity and metabolic syndrome in later life have been identified.

With the foregoing caveat notwithstanding, the thrifty genotype hypothesis derives strong support from empirical evidence indicating that genes are a major determinant of inter-individual variation in body weight and body fat mass in all species, including humans, and a close interaction between genes and environment determines the final phenotype of the individual. At present, the underlying relationship between maternal nutrition and its impact later in life is poorly understood; it is also

unclear whether the insulin signaling pathways in the fetus are reversible and thus capable of being fine-tuned in response to environmental stimuli during the period of postnatal development, and later in adulthood^[11].

In the June 2012 issue of the journal *Diabetes*, Garg *et al*^[12], describe a set of experiments to demonstrate the potential plasticity inherent in the fetal metabolic program elicited in response to intrauterine sub-optimal nutrition in rats. These investigators studied four groups of male rats: control rats without experimental caloric intervention (CON), intrauterine growth restricted rats that were allowed normal food intake during postnatal period (IUGR), normal rats that were subjected to reduced caloric intake during lactation (PNGR), and finally, animals that were maintained on combined IUGR and PNGR regimens (IPGR). The authors recorded body weight, visceral and subcutaneous fat mass, food and water intake for all four groups of animals, at the time of weaning, and at monthly intervals thereafter between the ages of 4 mo and 10 mo. Additionally, they measured plasma levels of glucose, insulin and leptin in the control and experimental cohorts.

The authors report that the IUGR group of animals, that experienced gestational under-nutrition followed by unrestricted postnatal caloric intake, gained the greatest body mass, as well as accumulated excessive subcutaneous and visceral fat. It was also noted that while food intake per body weight in IUGR rats was lower than in CON, the IUGR animals were metabolically inflexible, i.e., showed similar rates of energy expenditure and O₂ consumption (VO₂) in the fed and fasted states. However, to the authors’ surprise, the newborn IUGR rats were glucose tolerant and insulin sensitive like the control animals. The authors speculate that the observed metabolic phenotype of IUGR rats was consistent with their increased circulating levels of leptin. More importantly, they discovered that food restriction during lactation in rats that were nutritionally deprived *in utero* (PNGR) had a salutary effect on their metabolic state at 10 mo of age. Although the PNGR rats had a higher intake of food per body mass, their metabolic profiles were similar to those of CON and IPGR animals; thus PNGR rats elicited greater metabolic flexibility as judged by their ability to increase VO₂ and heat production during the fed state. It should also be pointed out that, as judged by the anthropomorphic and metabolic criteria used by Garg *et al*^[12], the IPGR rats were the most insulin sensitive, had a higher resting VO₂ and displayed greater physical activity level compared with animals in the CON, IUGR and PNGR cohorts.

The observation that postnatal caloric restriction (CR) superimposed on intrauterine under nutrition leads to an improved metabolic profile in rats that would otherwise develop metabolic inflexibility and visceral obesity is novel. However, the report of Garg *et al*^[12], differs from a number of previous studies that have claimed that the existence of insulin resistance was a common occurrence in IUGR rats^[13-16]. In a related report, it was shown that

the IUGR phenotype was also associated with decreased pancreatic β -cell mass^[17]. It should be noted however that Garg *et al*^[12] did not report the status of β -cell mass in their experimental cohorts.

The authors point out that an apparent discrepancy between their observations and those reported previously is likely due to methodological differences. The authors conclude that “it appears that none of these studies demonstrated changes in *in vivo* glucose utilization consistent with insulin resistance; rather some investigations demonstrated early insulin deficiency or relied on ratios between glucose and insulin to make conclusions regarding the presence of insulin resistance subsequently in the adult offspring.” I think this is a reasonable explanation for the discrepancy between the current publication and earlier reports that inferred insulin sensitivity in IUGR animals from the ratios between circulating glucose and insulin concentrations. The hyperinsulinemic-euglycemic clamp, as used by Garg *et al*^[12], is a more rigorous technique to demonstrate insulin sensitivity. The methodological differences notwithstanding, a key advance reported by Garg *et al*^[12] is that a propensity of rats exposed to intrauterine under-nutrition to develop obesity and metabolic syndrome could be attenuated by CR during the postnatal period. Although these authors have appropriately emphasized their observation supporting a salutary influence of postnatal CR on IUGR animals, in my opinion, their finding that postnatal CR had a measurable positive influence on the metabolic profile of all groups of rats, regardless of their nutritional status *in utero*, is also highly significant. Alas, these authors did not follow these animals long enough to determine if and when any of the animals develop serious insulin resistance and overt diabetes in future.

Since the developmental origins of obesity are poorly understood, the tantalizing observations of Garg *et al*^[12], have clear implications for future investigations. For example, it would be important to assess if and when the IUGR offspring on unrestricted access to calories go on to develop frank diabetes and metabolic syndrome. Similarly, the future studies should focus on the mechanisms by which CR modifies the propensity of IUGR rats for obesity and metabolic syndrome later in life. These mechanistic investigations need to be addressed at the genomic, proteomic and metabolomic levels. The observations in the rodent models also need to be extended to non-human primates to gain a deeper understanding of the evolutionary basis of how CR impinges on the genome of various species.

The epidemiological data strongly suggest that low-birth human infants have a higher tendency to become obese and diabetic during adolescence^[18]. Every year more than 20 million undernourished mothers give birth to babies weighing less than 2.5 kg; many of these would become obese and diabetic. The epidemic of obesity and impaired metabolic health, particularly in young adults, is likely to create an unprecedented burden on the healthcare systems of many societies. The observations of Garg *et al*^[12], have serious implications in term of the

design of the future translational studies in humans.

On a final note, although consistent changes in constitutive gene expression in the models of obesity and metabolic syndromes have been observed, the molecular mechanisms by which CR determines the phenotype of the newborn and its metabolic plasticity are far from clear. Much of what we have learned about CR has been from the genetic models of ageing such as yeast, *Caenorhabditis elegans* and fruit flies. These studies have demonstrated CR is associated with key changes in nutrient and energy sensing pathways, particularly those related to insulin signaling. Additionally, studies in model organisms have unraveled a role of the epigenetic mechanisms involving methylation of DNA and posttranslational modification of chromatin in metabolic re-programming. However, the exact nature of the “epigenetic codes” that determine metabolic plasticity remain to be defined^[11]. Finally, it is imperative that the analogous pathways be rigorously investigated in humans with a goal to discover drugs or nutrients that may mimic CR and a full spectrum of its health benefits^[19].

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Events Calendar 2012

January 15-17, 2012
ICADIT 2012: International conference on Advances in Diabetes and Insulin Therapy
Zurich, Switzerland

January 29-February 3, 2012
Genetic and Molecular Basis of Obesity and Body Weight Regulation
Santa Fe, NM, United States

February 3, 2012
The Future of Obesity Treatment
London, United Kingdom

February 8-11, 2012
5th International Conference on Advanced Technologies and Treatments for Diabetes
Barcelona, Spain

February 9-10, 2012
EC Conference on Diabetes and Obesity Research - Save the Date
Brussels, Belgium

February 21, 2012
Association of Children's Diabetes Clinicians 6th Annual Meeting
Coventry, United Kingdom

February 23, 2012
Diabetes and kidney disease: advances and controversies
Birmingham, United Kingdom

March 1-3, 2012
International conference on Nutrition and Growth
Paris, France

March 7-9, 2012
Diabetes UK Annual Professional Conference 2012
Glasgow, United Kingdom

March 15 -16, 2012
Monogenic Disorders of Insulin Secretion: Congenital Hyperinsulinism and Neonatal Diabetes
Philadelphia, PA, United States

March 15 -17, 2012
2012 DF Con - Diabetic Foot Global Conference
Hollywood, CA, United States

March 19-22, 2012
Society for Endocrinology BES 2012
Harrogate, United Kingdom

March 22-25, 2012
2nd Latin America Congress on Controversies to Consensus in Diabetes, Obesity and Hypertension
Rio de Janeiro, Brazil

March 29-31, 2012
The 4th International Conference on Advances in Diabetes and Insulin Therapy
Riga, Latvia

March 29-April 1, 2012
New Frontiers in Diabetes Management
Ocho Rios, Jamaica

April 2-6, 2012
6th Annual Primary Care Spring Conference: Session 1
Palm Coast, FL, United States

April 4-7, 2012
39th Panhellenic Congress of Endocrinology and Metabolism
Athens, Greece

April 11-13, 2012
ICDM 2012: International Conference on Diabetes and Metabolism
Venice, Italy

April 11-13, 2012
ICDHLSP 2012: International Conference on Diabetes, Hypertension, Lipids and Stroke Prevention
Venice, Italy

April 16-17, 2012
Paediatric and Adolescent Diabetes
Birmingham, United Kingdom

April 22-25, 2012
9th International Podocyte Conference
Miami, FL, United States

May 9-12, 2012
19th European Congress on Obesity
Lyon, France

May 23-27, 2012
AACE 21st Annual Scientific and Clinical Congress - American Association of Clinical Endocrinologists
Philadelphia, PA, United States

May 24-27, 2012
27th Annual Clinical Conference on Diabetes
Bonita Springs, FL, United States

June 8-12, 2012
American Diabetes Association's 72nd Scientific Sessions
Philadelphia, PA, United States

June 29-August 2, 2012
ESE Summer School on Endocrinology
Bregenz, Austria

August 1-4, 2012
AADE 39th Annual Meeting - American Association of Diabetes Educators
Indianapolis, IN, United States

September 13-16, 2012
EMBO-EMBL Symposium: Diabetes and Obesity
Heidelberg, Germany

October 1-5, 2012
48th European Association for the Study of Diabetes Annual Meeting
Berlin, Germany

November 7-9, 2012
40th Meeting of the British Society for Paediatric Endocrinology and Diabetes
Leeds, United Kingdom

November 8-11, 2012
The 4th World Congress on Controversies to Consensus in Diabetes, Obesity and Hypertension
Barcelona, Spain

December 4-6, 2012
1st American Diabetes Association Middle East Congress
Dubai, United Arab Emirates



INSTRUCTIONS TO AUTHORS

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Format

Journals

English journal article (list all authors and include the PMID where applicable)

- 1 **Jung EM**, Clevert DA, Schreyer AG, Schmitt S, Rennert J, Kubale R, Feuerbach S, Jung F. Evaluation of quantitative contrast harmonic imaging to assess malignancy of liver tumors: A prospective controlled two-center study. *World J Gastroenterol* 2007; **13**: 6356-6364 [PMID: 18081224 DOI: 10.3748/wjg.13.6356]

Chinese journal article (list all authors and include the PMID where applicable)

- 2 **Lin GZ**, Wang XZ, Wang P, Lin J, Yang FD. Immunologic effect of Jianpi Yishen decoction in treatment of Pixu-diarrhoea. *Shijie Huaren Xiaohua Zazhi* 1999; **7**: 285-287

In press

- 3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

- 4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

- 5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

No author given

- 6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

Volume with supplement

- 7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

Issue with no volume

- 8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; (**401**): 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

No volume or issue

- 9 Outreach: Bringing HIV-positive individuals into care. *HRS/A Careaction* 2002; 1-6 [PMID: 12154804]

Books

Personal author(s)

- 10 **Sherlock S**, Dooley J. Diseases of the liver and biliary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

Chapter in a book (list all authors)

- 11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

Author(s) and editor(s)

- 12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wiczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

Conference proceedings

- 13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

Conference paper

- 14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

Electronic journal (list all authors)

- 15 Morse SS. Factors in the emergence of infectious diseases. *Emerg Infect Dis* serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: <http://www.cdc.gov/ncidod/eid/index.htm>

Patent (list all authors)

- 16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

Statistical data

Write as mean \pm SD or mean \pm SE.

Statistical expression

Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as χ^2 (in Greek), related coefficient as *r* (in italics), degree of freedom as *v* (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

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Use SI units. For example: body mass, *m* (B) = 78 kg; blood pressure, *p* (B) = 16.2/12.3 kPa; incubation time, *t* (incubation) = 96 h, blood glucose concentration, *c* (glucose) 6.4 ± 2.1 mmol/L; blood CEA mass concentration, *p* (CEA) = 8.6 ± 24.5 μ g/L; CO₂ volume fraction, 50 mL/L CO₂, not 5% CO₂; likewise for 40 g/L formaldehyde, not 10% formalin; and mass fraction, 8 ng/g, *etc.* Arabic numerals such as 23, 243, 641 should be read 23 243 641.

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Italics

Quantities: *t* time or temperature, *c* concentration, *A* area, *l* length, *m* mass, *V* volume.

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