

Application of stable isotopic techniques in the prevention of degenerative diseases like obesity and NIDDM in developing societies

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Abstract

Economic development in developing societies characterized by industrialization, urbanization, and globalization has seen the emergence of an epidemic of diet- and life-style-related chronic degenerative diseases. A research project was initiated under the aegis of the International Atomic Energy Agency (IAEA), Vienna, Austria under its Coordinated Research Programme (CRP) to promote the use of stable isotopic techniques to document the extent of the problem and to understand the determinants of this epidemic. The principal objectives of this CRP involving countries both in the North and the South are to define the magnitude of the problem of obesity and non-insulin dependant diabetes mellitus (NIDDM) in developing countries, to identify the vulnerable groups at increased risk, and to attempt to describe the metabolic and physiological mechanisms underlying this phenomenon. These comparative international studies of obesity and NIDDM are looking at the effects of childhood malnutrition (Brazil) and socioeconomic differentials (Mexico)

on adult risk factors; the composition of the daily diet on obesity (Chile); levels of patterns of physical activity of older adults (China) as well as their influence on weight gain and obesity (Cuba, Nigeria); the impact of body composition and energy expenditure on the evolution of frank diabetes from impaired glucose tolerance (Jamaica), and of body compositional changes and the role of inflammatory cytokines on impaired glucose tolerance (India). The last study conducted in New Zealand was aimed at comparing the energy expenditures of Maori (Pacific Island) with New Zealanders of European descent.

Key words: stable isotopes, chronic diseases, obesity, non-insulin dependent diabetes, cardiovascular disease, insulin resistance, body composition, inflammatory cytokines, glucose tolerance.

Introduction

Non-communicable diseases (NCDs) account for nearly 60% of deaths globally mostly due to heart disease, stroke, cancer, diabetes, and lung diseases. The rapid rise of NCDs represents one of the major health challenges to global development in the 21st century and threatens economic and social development of nations as well as the lives and health of millions of their subjects. In 1998 alone, NCDs were estimated to have contributed to 31.7 million deaths globally and 43% of the global burden of disease [1]. Based on current trends, it is expected that by the year 2020, NCDs will account for 73% of deaths and 60% of the disease burden. A recent analysis of mortality trends from NCDs suggests that large increases in NCDs have occurred in developing countries [2], particularly those in rapid transition like China, Brazil, and India. The rapid increase in these diseases is seen disproportionately in poor and disadvantaged populations and is contributing to widening health gaps between and within countries. In 1998, of the total number of deaths attributable to NCDs, 77% occurred in develop-

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ing countries, and of the disease burden they represent, 85% was borne by low and middle-income countries [1]. This increase in the incidence of chronic degenerative diseases is due to a complex range of factors that interact to determine the nature and course of this epidemic [3].

As developing societies industrialize and urbanize, and as standards of living continue to rise, weight gain and obesity will pose a growing threat to the health of the citizens. Obesity is now widely prevalent in several developing countries, particularly those in rapid transition, and affects both children and adults, and is a significant contributor to the ill health of people in developing countries. Obesity is a key determinant and important risk factor for other NCDs such as non-insulin dependant diabetes mellitus (NIDDM), cardiovascular disease (CVD) including hypertension, and certain cancers. The increasing prevalence of obesity in a population in developing societies is an early indicator of an emerging health burden due to the increasing mortality and morbidity from NCDs.

The principal objectives of this Coordinated Research Programme (CRP) of the International Atomic Agency (IAEA), Vienna Austria; involving countries both in the North and the South are to define the magnitude of the problem specifically of obesity and non-insulin dependant diabetes mellitus (NIDDM) in several developing countries, to identify the vulnerable groups at increased risk, and to attempt to describe the metabolic and physiological mechanisms underlying this phenomenon. This CRP was set up with the following objectives:

- » to promote the use of stable isotopic techniques to document the extent of the problem and to understand the determinants of obesity and non-insulin dependant diabetes mellitus (NIDDM) in developing societies,
- » to define the magnitude of the problem of Obesity and NIDDM in developing countries,
- » to identify the vulnerable groups at increased risk and to attempt to describe the metabolic and physiological mechanisms underlying this phenomenon, and
- » to enhance North-South collaboration and transfer of know-how and technology.

The following sections of this paper provide information on each of the studies under this IAEA-CRP Investigative Programme country by country while the principal objectives of these studies are summarized in the table 1.

Brazil

The studies in Brazil were conducted by A. Sawaya and her colleagues at the Department of Fisiologia, Disciplina de Neurofisiologia e Fisiologia Endocrina,

Universidade Federal de Sao Paulo, Sao Paulo, Brazil [4] and in partnership with S. Roberts at the USDA HNRC at Tufts University, Boston. Previous studies by this group demonstrated higher energy conservation mechanisms in marginally stunted Brazilian children exemplified by lower resting metabolic rates, lower fat oxidation, higher susceptibility to gain weight, and thus leading to a higher prevalence of stunted but obese individuals. The hypothesis being tested was that living in shantytowns in the city of Sao Paulo, Brazil impairs growth and increases risk of stunting and that this stunting may be associated with alterations in fat patterning, circulating hormones such as insulin and IGF-1 as well as alterations in plasma lipid profiles. The study recruited 58 children of both sexes aged 8 to 11 years out of a total of 300 who were screened from a shantytown in Sao Paulo, half of whom were stunted and the other half had normal height-for-age (HAZ). Stunted children ($n = 28$ with HAZ Z scores < -1.5) were compared to normal children ($n = 30$ with HAZ Z scores > -1.5). About 98% of the population had low IGF-1 values indicating impaired growth. The stunted boys and girls demonstrated delayed Tanner stages of pubertal development and had lower systolic blood pressures, but higher diastolic blood pressures. Alterations in insulin profile by homeostatic model assess-

TABLE 1. Comparative international studies of obesity and NIDDM under the IAEA-CRP in developing countries

Developing countries	Objective of IAEA-CRP Investigation
Brazil	The effects of childhood malnutrition on adult risk factors
Mexico	The effects of socioeconomic differentials on adult risk factors
Chile	The composition of the daily diet specifically fatty acids in the diet on obesity
China	The physical activity of adults as risk factors for overweight and obesity
Cuba	Total energy expenditure as risk factors for chronic disease in older adults in rural communities.
Nigeria	The influence of physical activity on weight gain and obesity
Jamaica	The influence of physical activity on the evolution of frank diabetes from impaired glucose tolerance
India	Body composition and the role of inflammatory cytokines on impaired glucose tolerance
Maori and Pacific Island	Comparison of energy expenditure of Maori and Pacific Island with New Zealand adults of European descent

ment (HOMA) analysis manifested by lower fasting insulin, higher insulin sensitivity, and lower IGF-1 levels characterized the stunted children. The plasma lipid profile was not different between the two groups. It was concluded that the environment in shantytowns impairs growth potential and that stunted children growing up in these environments have abnormal beta cell function and lower fasting insulin and higher insulin sensitivity.

Mexico

The Mexican studies on the risk factors for NIDDM and cardiovascular disease in adults from different socioeconomic levels was lead by Mauro Valencia Juillerat, at the Centro de Investigacion en Alimentacion y Desarrollo at Hermosillo, Sonora, Mexico [5]. The earlier National Survey of Chronic Disease in Mexico involving 18,924 adults in 8,120 households throughout Mexico [6] found a relationship between educational achievement and prevalence of NIDDM, i.e., 15.6% prevalence in those with no education compared with 2.8% among postgraduates. The present study was conducted on 350 male and female adults over 20 years old in Hermosillo, Mexico. They were recruited from low- and high-income socioeconomic groups. The subjects provided blood samples for an oral glucose tolerance test (OGTT) and for plasma lipids, insulin, and leptin determinations. The prevalence of obesity (BMI > 30) in this sample of the 350 adult men and women was in 23.4%, and it was observed that subjects with abnormal glucose levels had higher body weight, BMI, weight-for-height (WH), % fat, and blood pressure than normo-glycemic subjects. Subjects with high central adiposity (combination of % fat and WH ratio) had higher triglycerides, 2-hour glucose levels, and lower HDL-cholesterol. Waist circumference, WH, BMI, and bio-impedance analysis (BIA) for body composition showed the best correlations with glycemic status, blood lipids, and insulin sensitivity. Detailed body composition studies comparing deuterium dilution with data from other measurements and analysis of physical activity patterns between the two income groups and their relationship to adult risk factors is in progress.

Chile

The role of the composition of the daily diet and more specifically the fatty acids in the diet on the risk of obesity was investigated by Eric Diaz and colleagues [7] at the Energy Metabolism and Stable Isotopes Laboratory, Institute of Nutrition and Food Technology (INTA), University of Chile, Santiago, Chile. The hypothesis is that the type of fatty acids ingested in

the diet can modify the disposal of lipids in the body, and that this may be an additional factor in worsening the insulin resistance. The effects of changes in dietary fatty acid composition on macronutrient oxidation were studied in eight normal weight and six obese adult women between 30 to 45 years old. The study followed a cross-over design of one baseline measurement and two week periods of supplementation with either canola oil or sunflower oil with a washout period in between followed by the other oil. The intervention trial comparing sunflower oil with canola showed significant modifications of plasma fatty acid profiles depending on the oil supplemented. No differences were observed between controls and obese. However the control subjects had higher fat oxidation with sunflower compared to canola treatment, while the obese women showed higher carbohydrate oxidation associated with a greater insulin response during the sunflower treatment. Significant changes in plasma n6/n3 fatty acids (n6/n3) ratio were observed. The higher fat oxidation in controls was associated positively with changes in plasma n6/n3 ratio while the higher insulin response in the obese was not associated with changes in plasma n6/n3 ratio.

China

The risk factors for obesity in Chinese adults with obesity, an important public health concern in China, was investigated by Guansheng Ma at the Institute of Nutrition and Food Hygiene, Chinese Academy of Preventive Medicine, Beijing, China [8]. The basic premise for this investigation was the recognition that dietary energy and fat intakes and physical activity levels play a critical role in overweight and obesity, which in turn is a risk factor for hypertension and NIDDM. The objectives of the study were to compare dietary intakes, physical activity patterns, anthropometry, and plasma insulin, leptin, and lipid profiles between normal weight, overweight, and obese adults based on BMI. The study included 152 adults 35 to 52 years old of both sexes. Overweight and obese groups in China have significantly greater BMI, waist, hip, waist/hip ratio, and percent of body fat than the normal weight group. Their total energy and fat intakes were greater than those of the normal weight group, while they expended much less energy. The obese had a significantly higher risk of hypertension, and had higher fasting insulin and leptin levels than the normal weight group.

Cuba

The IAEA CRP in Cuba investigated the energy requirements and physical activity levels of active elderly adults in rural areas. This investigation was lead by Manuel

Hernandez-Triana of the Institute of Nutrition and Food Hygiene at Havana, Cuba [9]. The collaboration was South-South with INTA in Chile. Elderly subjects aged 60 to 74 years ($n = 48$) in a rural mountain community of Western Cuba (Las Terrazas) were studied. Of those, 40% had impaired glucose tolerance and 23% had hypertension. Estimates of total energy expenditure (TEE), as determined by the doubly-labeled water (DLW) method and physical activity levels (PAL) were much higher than that reported for similar age groups in other studies, while PALs estimated from questionnaires underestimated TEE as compared to PALs measured by the DLW method. Dietary energy intakes were underestimated by 11% for women and by 55% for men compared to TEE by DLW.

Nigeria

This investigation on the relative contributions of energy expenditure on physical activity, body composition, and weight gain to the evolution of impaired glucose tolerance into frank diabetes was carried out at the Department of Paediatrics & the Institute of Child Health, University College Hospital, Ibadan, Nigeria [10]. The investigation was lead by Adeyemo in Nigeria and is another example of South-South collaboration and cooperation under the IAEA CRP program as this study in Nigeria is linked with Tropical Metabolism Research Institute (TMRU) in Jamaica. A one year follow-up of a lean cohort of adults (BMI ~21–22) in Nigeria showed an increase in body weight and BMI, an increased prevalence of overweight from 21.3% to 23.9%, an increased prevalence of obesity from 5.2% to 7.7%, and an increased body fat (fat mass and percent body fat mass). There was also a change in physical activity levels with increased fasting insulin and insulin-glucose ratios but no increase in homeostatic model assessment-insulin resistance (HOMA-IR). The body weight changes occurred without any worsening in the glycemia status. The conclusions are that the population is yet to reach the BMI threshold above which worsening of glycemia status accompanies the increases in weight gain. A further follow-up over several years would be required.

Jamaica

A similar follow-up of adults to examine the relative contributions of energy expenditure on physical activity, body composition, and weight gain to the evolution of impaired glucose tolerance into frank diabetes was being carried out at the Tropical Metabolism Research Institute (TMRU), University of West Indies, Mona, Kingston, Jamaica [11]. This investigation was lead by Terrence Forrester with a collaborator (Farook Jahoor)

in the North at the USDA Children's Nutrition Research Center, Houston, Texas. In a sample of 614 adults (239 men and 375 women) anthropometry and body composition, energy expenditure budgets and OGTTs were carried out. A follow-up four years later of the cohort of urban Jamaican adults showed that the prevalence of impaired glucose tolerance (IGT) and frank diabetes increased over the same period. Lower physical activity was significantly associated with poorer glucose tolerance status. All adiposity variables, e.g., BMI, percent fat, and waist circumference predicted worsening of glucose tolerance for men while change in waist circumference predicted worsening status in both men and women. It was concluded that interventions to improve levels of physical activity are crucial to reduce the burden of chronic diseases including obesity and NIDDM.

India

The IAEA CRP contract in India was lead by Chittaranjan Yajnik at the King Edward Memorial (KEM) Hospital research center in Pune. The relationships between total body fat, plasma pro-inflammatory cytokines and their role in insulin resistance in Indians was investigated [12]. Like the study in TMRU, Jamaica this study also establishes a South-South Collaboration with St Johns Medical College, Bangalore with Anura Kurpad and All India Institute of Medical sciences (AIIMS) New Delhi with Anoop Misra. It also has North-South collaboration with John Yudkin at University College, London and Prakash Shetty at the London School of Hygiene & Tropical Medicine. The hypothesis for investigation was that the excess risk of insulin resistance in urban as compared to rural populations in India was the result of increased total body fat in the former, and that the increased total body fat resulted in insulin resistance which is mediated by changes in circulating pro-inflammatory cytokines. Studies in Pune, India in three different communities (rural/urban, slum/urban, middle-class) showed that the prevalence of obesity and central obesity (deposition of adipose tissue centrally distributed around the abdomen) progressively increased from rural to urban slums to urban middle-class men. This was reflected in an increasing prevalence of diabetes (0, 4% and 10%), impaired glucose tolerance (9%, 12%, and 20%), hypertension (2%, 4%, and 10%), and plasma cholesterol and triglyceride levels, respectively. The percentage of body fat was a significant predictor of increasing cardiovascular risk in these populations; central obesity increased the risk further, although to a smaller extent. The study concluded that measurement of body fat and its central distribution by appropriate isotopic and other methods should form an essential part of further studies of insulin resistance and cardiovascular disease risk in South Asians.

Maoris and Pacific Islanders

Elaine Rush of the Auckland University of Technology, New Zealand led the IAEA-CRP investigation on central obesity and risk for NIDDM in Maori, Pacific Island, and European young men in New Zealand [13]. This study compared the characteristics of normoglycemic young men 18 to 27 years old of Maori, Pacific Island, and New Zealand European descent ($n = 10$ in each group). An increased body fat content and central obesity were associated with measurements of glucose, insulin, lipids, and leptin indicating an increased risk of NIDDM. Central obesity was negatively associated with dietary fiber intake. TEE data using the DLW method are in the process of being analyzed. Body fat content and distribution of body fat predicted at a young age the increase in risk of NIDDM in all three ethnic groups. Further investigations are required to investigate differences between groups.

Conclusions

The following conclusions can be arrived at from the preliminary data from several investigations in countries in Latin American and the Caribbean, African, and Asian, and the Far Eastern regions of the developing world:

- » This IAEA-CRP offered a unique opportunity to study physical activity, body composition in relation to insulin resistance (NIDDM risk), and obesity risk in seven different countries (table 1) using stable isotopic and other techniques to investigate physical activity patterns, total energy expenditure, body composition, and anthropometric characteristics.
- » The IAEA-CRP provided an opportunity to use standardized protocols for body composition and physical activity measurements as risk factors for chronic diseases (obesity and NIDDM) in several developing countries despite variations in age, ethnicity, and geographic locations of the study populations.
- » The preliminary results of this IAEA-CRP activity confirmed the increasing risk of obesity and NIDDM in developing societies due to changes in diet and physical activity patterns and suggest that total body fat and its topography are perhaps the most important predictors of the evolution of insulin resistance syndrome.

The current IAEA-CRP program on the application of stable isotopic techniques in the prevention of degenerative diseases like obesity and NIDDM in developing societies demonstrates, in addition, that both North-South and South-South collaboration and cooperation can be very successful under international programs like these.

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